IMPROVING MEDICATION ADHERENCE

A BEHAVIOURAL SCIENCE APPROACH

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1 CHAPTER 1

1.1 Introduction

Recent developments in behavioural science provide us with a grounded approach to understanding and encouraging human behavioural change. Built on a strong scientific heritage, it draws on insights and methods from psychology, economics and neuroscience. Fundamentally, it challenges the view that people always behave with a rational self-interest. Evidence shows that people often make decisions intuitively, effortlessly and with little conscious awareness. These decisions encompass a wide variety of biases and rules-of-thumb with practical and often have severe implications in efforts to facilitate behaviour change. An understanding of behavioural science provides a practical approach to overcoming barriers to behaviour change.

Many of the biggest health problems that society faces are due to behavioural risk factors. Non-communicable diseases, such as cardiovascular disease and cancer, are the leading causes of death worldwide and caused by avoidable lifestyle choices like smoking, an unhealthy diet and physical inactivity. Similarly, as patients are given more control over their care, they often fail to follow agreed treatment despite explicit benefits.

It is commonly assumed that the people who are making poor decisions about their health are indeed making an active decision to do so. This means that people are consciously and intentionally making poor decisions about their health. We often compute intention from action and conclude that these people are either unwilling to change their behaviour or that they are unable to do so. The default solution to changing

people's behaviour therefore has been that since people act in their rational self-interest if we only tell people about the adverse consequences of their mis-behaviour they would change it. In reality however, just giving people information does not bring about the desired behaviour change. Through insights from behavioural science, we can develop a better understanding of how and why people behave the way they do which can lead to a better informed design of health behaviour change interventions.

In this PhD thesis, I aim to examine one healthcare problem where I believe the application of insights from behavioural science can create a meaningful impact. This problem relates to the issue of medication adherence. In particular, I am interested in adherence to antibiotic medication.

Adherence is the extent to which the patient's behaviour matches agreed recommendations from the prescriber. Several reviews have found that adherence among patients in developed countries is only 50% (Horne et al, 2005; Haynes et al, 2002; WHO, 2003). Yet this figure is high in comparison with developing countries. For example, in United States, 51% of the patients with hypertension adhere to their medication. While in developing countries such as Gambia, Seychelles and China, only 27%, 26% and 43% of patients with hypertension adhere to their antihypertensive medication regimen (Bovet P et al., 2002; Graves JW., 2000; van der Sande MA et al., 2000; Guo H et al., 2001). Although adherence depends on a lot of factors, there is consistent evidence that regardless of what is being treated; non-adherence is a significant problem (WHO, 2003). The most recent systematic review on medication adherence concludes that: "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in

specific medical treatments." (Horne et al, 2005). In this PhD thesis, I therefore turn my attention to improving the effectiveness of adherence interventions.

The medication adherence problem that I am focusing on is the kind where patients have a certain curable disease (e.g. Tuberculosis); they are experiencing the symptoms of that disease (e.g. weight loss, blood in cough etc.) and when the patients start taking the medication the symptoms disappear sooner than the elimination of the disease. As the symptoms disappear sooner than the disease, the patients are feeling *'all better now'* and many of them tend to stop taking their medication. In medical terms, a patient is said to '**Default**' if he/she fails to adhere to the medication course. As patients Default to their medication course, the process of elimination of the disease from their bodies remains incomplete (O'Neill, 2016).

Many patients stop taking their medication once symptoms disappear

1.2 Literature Review

1.2.1 What is the problem?

A major obstacle to achieving efficient control of diseases is attributed to poor adherence to treatment by patients (Thiam et al., 2007). This remains a common problem in spite of various interventions which are aimed at improving treatment completion (Munro et al., 2007). An estimated 20 – 50 % of patients fail to complete therapy (Cuneo & Snider, 1989). In cases where medical treatment is complex or lasts an extended time, patients often fail to adhere to their medication as they have been instructed (Munro et al., 2007). New and innovative strategies are essential to successfully improve patient adherence to treatment.

1.2.2 Why is it a problem? Why is adherence necessary?

The apparent recovery achieved upon partial completion of the course of treatment convinces patients that it is acceptable and harmless to discontinue taking their medication. However, discontinuation of treatment may put patients at risk of relapsing (CDC, 1999).

Neglecting to ensure compliance with treatment advice can lead to grave problems. For instance, non-adherent patients are likely to remain sick, spread the disease to uninfected persons, develop and possibly spread drug-resistant strains of the disease, be faced with prolonged and more expensive therapy and may even die due to interrupted treatment (CDC, 1999). Interrupted treatment therefore presents a threat not only to the individual, but to the wider community (Volmink & Garner, 2006).

The spread of drug resistant strains (also referred to as Antimicrobial Resistance or AMR in short) of the disease has been shown to be one of the most significant problems of those mentioned above. There is already a rise of drug resistant infections with numbers suggesting that up to 50,000 lives are lost each year to antibiotic-resistant infections in Europe and the US alone. Globally, at least 700,000 die each year of drug resistance in illnesses such as bacterial infections, malaria, HIV/AIDS or tuberculosis. KPMG and RAND carried out a scenario analysis looking at what the world would look like in 2050 if the status quo is maintained and concluded that without any policies and effort to stop AMR, by 2050 we will have more than 10 million deaths every year due to AMR (O'Neill, 2016). A detailed discussion around AMR can be found in Appendix 8.4.

The social impact of non-adherence has been quantified through a 'top-down' approximation. This method uses aggregate data on mortality, morbidity, hospital admissions, disease related costs and other healthcare relevant data to generate estimates of economic cost of non-adherence (Liu et al, 2002). The annual cost of non-adherence to the UK Government is £150 million resulting in wasted medicine, re-admissions etc., for the US this figure is over $1 billion (Horne et al., 2005).

In response to the problem created by non-adherence to medicinal treatment, numerous studies have been undertaken in attempts to remedy this gaping obstacle to global health. Acknowledgment of the behavioural nature of the issue has facilitated the development of several manners of behaviour modification in efforts to reduce the percentage of non-adherent patients. The difficulty experienced by such a vast percentage of patients following their treatment regimens has raised awareness of

adherence as a complex behavioural issue which is influenced by many factors (Munro et al., 2007).

1.2.3 Factors contributing to non-adherence

1.2.3.1 Personal and Cultural beliefs

Many patients hold their own personal and/or cultural beliefs regarding the manner in which they should be treated. Where the prescribed course of action against the disease conflicts with these views, patients may become reluctant to adhere to a regime they feel is ineffective. This leads to alienation of the patient from the health care workers, further decreasing their chances of an effective recovery (CDC, 1999).

1.2.3.2 Relationship between Patients and Clinical Team

Poor relationships with health care workers can negatively impact upon patient adherence; if patients have a comfortable level of confidence in their health care workers, they are more likely to follow instructions and cooperate with treatment. A focus on communication with patients, particularly regarding expected side effects and the management of these side effects help build a positive and trusting relationship between the patient and the health care provider (Chesney, 2003). Another aspect of the relationship barrier is the misjudgement of doctors about the adherence rate of patients.

1.2.3.3 Physical, Social & Mental limitations

Some patients do not possess the necessary skills for accurately adhering to a prescribed regimen of treatment and are unable to follow the instructions provided to them by health care workers. For example, elderly patients with limited mobility, patients

suffering from substance abuse, those with poor mental health and small children are all groups placed at a greater risk of having problems with adherence (CDC, 1999).

1.2.3.4 Lack of Knowledge

A lack of knowledge and awareness about the disease and its recommended treatment also contributes to non-adherence. It is often the case that patients have not been made to fully comprehend the treatment, the manner in which they must proceed to take their medication or the importance and need for such a long period of treatment (CDC, 1999).

1.2.3.5 Lack of motivation

Patients' lack of awareness may lead to de-motivation for the completion of treatment. Further, an absence of symptoms acts as a signal for patients that they are all well which reduce their motivation to complete their treatment. Such a lack of motivation may also occur where the patient has a number of priority issues with which he must contend (CDC, 1999).

1.2.4 Interventions to improve adherence rate

There have been four recent systematic reviews of interventions for medication adherence with mixed results (Haynes et al., 2002; Roter et al., 1998; Peterson et al., 2003; Horne et al., 2005). The interventions reviewed were generally effective and the adherence rate increased by 4% to 11% among different interventions. However, the reviews found many interventions that failed to achieve the desired outcome.

The interventions to improve medication adherence can be divided into five categories: 1. Reinforcement: make treatment environments more appealing, 2. Education: communication information about best practice, 3. Provider support: direct educational

or behavioural strategies at healthcare staff, 4. Affective: change emotional or social influences through counselling or social support and 5. Behavioural: improve a patient's capacity to deal with taking medication.

My focus in this dissertation is on the last category.

1.2.5 Most behaviour change interventions to address adherence have not been successful because they lacked theory

It was highlighted in the previous section that the systematic reviews on interventions to improve medication adherence found that the results of the interventions were quite mixed i.e. many interventions failed to achieve the desired outcome. Horne et al (2005) argued that one reason for the interventions to have decreased effectiveness was the lack of use of appropriate theoretical models to develop the interventions systematically. Furthermore, most of the interventions were neither modelled nor piloted to really understand the underlying mechanisms that drive the non-adherence behaviour (as recommended by the Medical Research Council in their framework to develop complex interventions to effect behaviour change which is discussed in the next section).

Developing behaviour change interventions that lack an underpinning theoretical framework poses a problem as it does not allow the researcher and the user of that research to identify which specific behaviour change process are responsible for observed change (Michie et al.,2005). Even if we know which interventions work, without a theoretical underpinning we would not really know why or how they worked. Furthermore, because one cannot draw a general understanding of what works and what doesn't, it is difficult to translate the learning to future research.

1.2.6 How behaviour change interventions should be developed

I discussed in the last two sections how the systematic reviews have found that the interventions to improve medication adherence have had mixed results and one of the reasons has been that the interventions were not developed systematically (I discuss the need to have systematically developed and theoretically informed behaviour change interventions in detail in the next chapter). Perhaps the most well developed account of how behavioural change interventions should be designed is provided by the UK's Medical Research Council. They have developed a guideline outlining the steps that should be taken to design behaviour change interventions systematically. In this section, I outline the approach that has been suggested by the Medical Research Council. I have followed this guideline for my research.

The Medical Research Council proposes that the development of a behaviour change intervention should follow the same cycle as drug development: (1) a theory behind the design of behavioural intervention; (2) followed by modelling of the problem and/or behaviour; and (3) finally a RCT and implementation of the intervention (MRC, 2006).

1.2.6.1 Theory stage

It is often the case that interventions developed to bring about behaviour change offer limited practical value as they lack a theoretical basis for the selection and development of the intervention (Michie et al., 2004). The Medical Research Council proposes that an important early task for a researcher is to develop a theoretical understanding of the underlying process and constructs that might bring about behaviour change. This helps in clearly understanding how successful interventions have had their effect, that is, which behaviour change processes can be attributed for the observed change. A

theoretical underpinning further allows the researcher to argue for the basis of selecting a particular intervention (MRC, 2006).

1.2.6.2 Modelling stage

The Medical Research Council proposed the 'Theory' stage to be followed by a 'Modelling' stage which can be considered as an equivalent to testing with rats in the drug development cycle. Modelling allows the researcher to investigate and identify the exact mechanisms that are bringing about the behaviour change. It makes possible the study of isolated effects of different interventions. Modelling thus allows the researcher to bottle the phenomenon and create knowledge about the underlying mechanisms of behaviour change that might be quite difficult to uncover otherwise (MRC, 2006). I explain in detail the benefits of having a modelling stage later in Section 5.1.

1.2.6.3 Randomised Control Trial (RCT)

Once a clear understanding of what works and what doesn't has been achieved through the modelling stage, the Medical Research Council finally proposes that a RCT be carried out to empirically test the intervention. Factors such as size and timing of effects; feasibility and acceptability of experimentation; and costs etc. are encouraged to be considered in this stage (MRC, 2006).

In this dissertation, I focus on the first two stages ('Theory' and 'Modelling') for developing behaviour change interventions to increase patient's adherence to antibiotic medication.

2 CHAPTER 2: Theory stage

One reason for the diminished practical value of much research related to the changing of professional behaviour is that there is an insufficient theoretical base for the development of these interventions

There can be many competing or partially overlapping theories that can help explain the likely process of change. Theoretical Domains Framework (TDF) was developed to overcome this challenge by providing behaviour change researchers with an integrative framework of theories of behaviour change. In this chapter I explain the 'Theoretical Domains Framework' which I used as the theoretical basis for my research. The MRC's guideline on developing complex behaviour change interventions also suggests among others using the 'Theoretical Domains Framework' for the theory stage.

2.1 Original Theoretical Domains Framework

Multitudes of studies are published in the domain of evidence based practice (EBP); however, often the interventions suggested are not implemented effectively resulting in less than desired health outcomes. Michie et al (2004) suggest that the mixed results and limited practical value of many of these interventions may be due to limited theoretical basis for the selection and development of interventions. Michie et al (2004) argue that behaviour change researchers should have access to a fixed set of theoretical constructs that explain behaviour change followed by a mechanism to identify which constructs are relevant to the given problem at hand.

A large number of studies about the effectiveness of guideline dissemination and implementation strategies have been identified, where the main behaviour change

methods used have been intuitive or educational. In this volume of literature, there does not appear to be a basis for ascertaining the most effective of these procedures as it is unclear which behaviour change processes can be credited with any observed change.

In light of the numerous studies done, a number of theoretical models explaining behaviour change have arisen. Despite the multitude of theories, they have not proven to be of great benefit to the issue at hand. The inability to provide for a sufficiently sound basis for any of the theories arrived at means that though they are many, they are not of great use. Michie et al. asserts that a definitive set of theoretical explanations and a means of identifying which are relevant to specific contexts is necessary.

There are also numerous psychological theories where a single construct may then be separated into multiple constructs. The problem which arises out of this is similar to that mentioned in the preceding paragraph, where there are then too many theoretical bases to effectively choose and apply psychological theories. The convoluted nature of these theories requires a greater effort in simplification in order to make them more useful. Psychological theories relating to explanations of behaviour change, rather than those which predict behaviour change, are more likely to assist in the identification of opportunities for interventions.

Three groups were invited to be part of the project and were inclusive of the main group of health psychology theorists, a multidisciplinary group for feedback on the approach to health service research and a psychological group.

The main working group comprised of 18 UK health psychologists who were tasked to brainstorm and identify as many psychological theories and theoretical constructs

relevant to behaviour change and implementation. Furthermore, this group then simplified the theoretical constructs into theoretical domains and evaluated the importance of each domain. The second group was enlisted to provide feedback on this list of construct domains and was comprised of 16 researchers, from a collaboration funded by the UK Medical Research Council. The third group of health psychologists was included to carry out a backward validation exercise.

The project was carried out in a series of five meetings during the period May 2003 – July 2004 and consisted of six stages. Psychological theories and theoretical constructs were identified in the first stage of the work. This included 33 psychological theories and 128 explanatory constructs for behaviour change.

The second stage involved participants' prioritization of three of the identified constructs and theories as relevant to the understanding and changing of behaviour and the intervention to change behaviour. These prioritized theories were then grouped into core 'domains', which was defined as a grouping of similar constructs. The final agreed list of theories and constructs were then assigned to a domain to which it was deemed relevant. The initial list of agreed domains which represented the prioritised constructs was made up of the following: Nature of behaviour ("what needs to be changed"), Knowledge and skills, Goal intention ("what to aim for"), Beliefs about consequences, Beliefs about own capabilities, Goal plan ("how to achieve change"), Environment–social, Environment–physical, Stress /emotion and "Other".

The third stage saw the participants evaluate the list of agreed upon theoretical domains to ascertain coherence and prevent redundant or overlapping constructs. Upon analysing this new list against the theories and constructs identified in the first stage, it

was agreed that two more construct domains were necessary: “memory, attention and decision processes” and “beliefs about EBP/guidelines”.

In the fourth stage, the domains were then assessed with regard to their specific value to health service researchers. The domains were then ranked in order of importance to influencing behaviour as agreed upon by a group of leading psychologists in the United States.

In the fifth stage of the research, having formulated and simplified the amalgamation of constructs into domains, the backward validation exercise as mentioned above was undertaken. This process led to a further refinement of the domain listing and was able to provide reassuring validation of the agreed list of domains. Some additional constructs were also identified for each domain.

The final stage involved both the theory and the health service researcher groups, formulating interview questions which would assess the nature of the behaviour change required and identification of the domain which was important to the behaviour change process which was necessary. Open and closed questions were used. Role plays and field tests of the agreed questions were carried out and were able to afford valuable insight into the most relevant domains. The feedback received was used to compile an amended set of interview questions.

The final outcome of the project was a framework grounded in psychological theory referred to as “Theoretical Domains Framework”. 12 theoretical domains were agreed upon for consideration when trying to understand health behaviour change problems. These domains were: (1) Knowledge (2) Skills, (3) Social/professional role and identity,

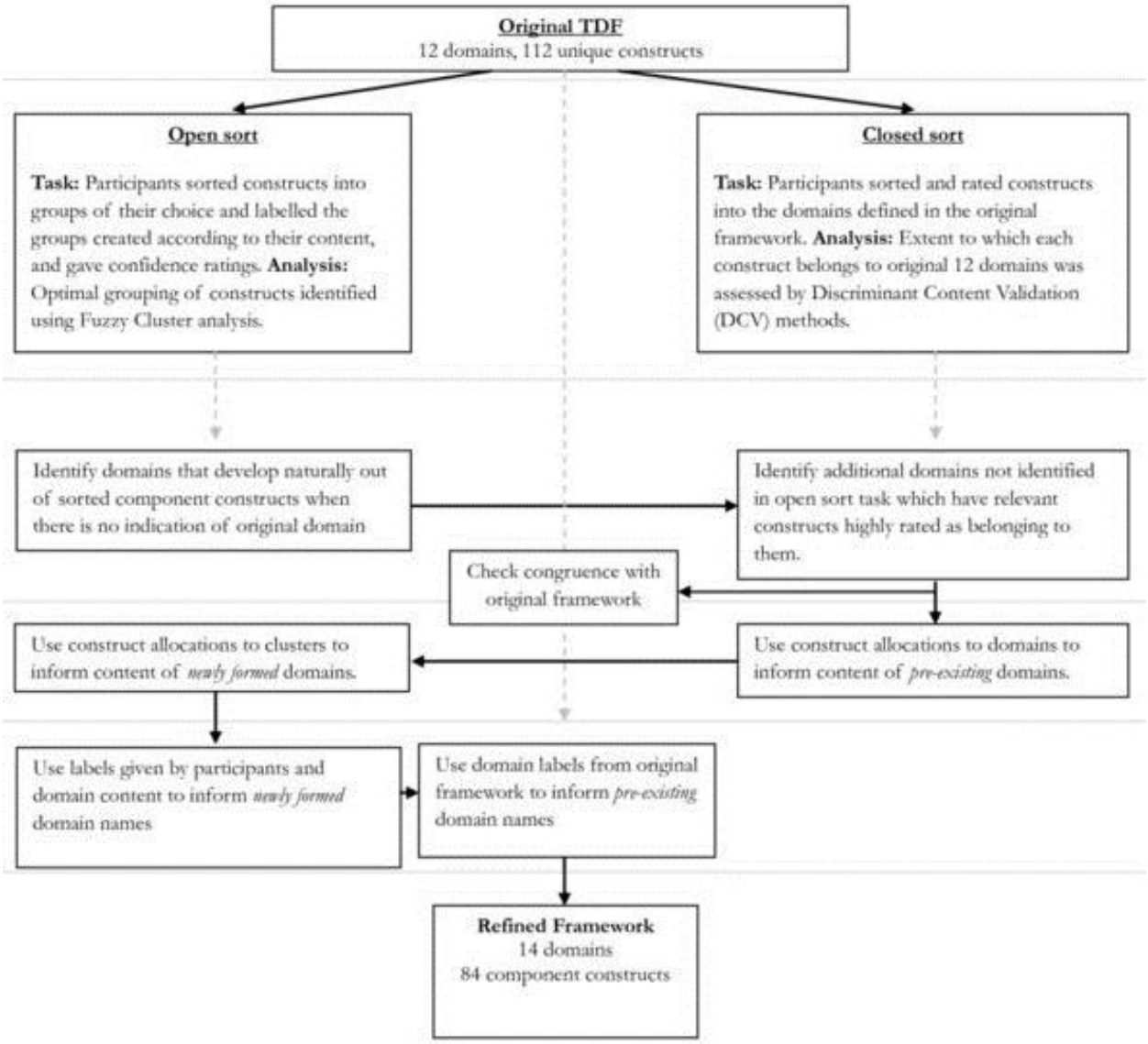
(4) Beliefs about capabilities, (5) Beliefs about own consequences, (6) Motivation and goals, (7) Memory, attention and decision processes, (8) Environmental context and resources, (9) Social influences, (10) Emotion, (11) Behavioural regulation, (12) Nature of behaviours.

The final listing included four additional domains to those identified by Fishbein et al as related to the promotion of HIV preventive behaviour. This may have been due in part to the increased expertise of this group as well as the developments in research literature since the 1991 Fishbein et al study. The need for describing and defining the behaviour which needs to be altered has been found to be of great importance in order to identify the relevant construct domains which may explain the basic behavioural processes. The domain list affords researchers with a guide to explanations of behaviour and behaviour change instead of a theoretical explanation of the behaviour itself. It has also been asserted that the domains listed might be able to give insight into the processes which underlie already existent non-theory based interventions. It is expected that a deeper and clearer comprehension of underlying processes will then provide more effective guidance for the development of interventions.

2.2 Validated Theoretical Domains Framework

Cane et al. (2012) carried out a validation exercise of the Theoretical Domains Framework and refined the original version to comprise of 14 domains of theoretical constructs which are as follows: (1) Knowledge (2) Skills, (3) Social/professional role and identity, (4) Beliefs about capabilities, (5) Optimism, (6) Beliefs about own consequences, (7) Reinforcement, (8) Intentions, (9) Goals, (10) Memory, attention and decision processes, (11) Environmental context and resources, (12) Social influences,

(13) Emotion, and (14) Behavioural regulation. The figure below has been taken from Cane et al. (2012) and it lays out the steps that were taken for the validation exercise.



Steps taken to validate the Theoretical Domains Framework (TDF)

The 14 domains of the TDF, their definitions and the constructs that fall under these domains are tabled below (All definitions are based on definitions from the American Psychological Associations' Dictionary of Psychology, and the table has been extracted from Cane et al. (2012)).

Domain (definition)	Constructs
1. Knowledge (An awareness of the existence of something)	Knowledge (including knowledge of condition /scientific rationale) Procedural knowledge Knowledge of task environment
2. Skills (An ability or proficiency acquired through practice)	Skills Skills development Competence Ability Interpersonal skills Practice Skill assessment
3. Social/Professional Role and Identity (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	Professional identity Professional role

	Social identity
	Identity
	Professional boundaries
	Professional confidence
	Group identity
	Leadership
	Organisational commitment
4. Beliefs about Capabilities (Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)	Self-confidence
	Perceived competence
	Self-efficacy
	Perceived behavioural control
	Beliefs
	Self-esteem
	Empowerment
	Professional confidence
5. Optimism (The confidence that things will happen for the best or that desired goals will be attained)	Optimism
	Pessimism
	Unrealistic optimism
	Identity

6. Beliefs about Consequences (Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)	Beliefs Outcome expectancies Characteristics of outcome expectancies Anticipated regret Consequents
7. Reinforcement (Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)	Rewards (proximal / distal, valued / not valued, probable / improbable) Incentives Punishment Consequents Reinforcement Contingencies Sanctions
8. Intentions (A conscious decision to perform a behaviour or a resolve to act in a certain way)	Stability of intentions Stages of change model Transtheoretical model and

	stages of change
9. Goals (Mental representations of outcomes or end states that an individual wants to achieve)	Goals (distal / proximal) Goal priority Goal / target setting Goals (autonomous / controlled) Action planning Implementation intention
10. Memory, Attention and Decision Processes (The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)	Memory Attention Attention control Decision making Cognitive overload / tiredness
11. Environmental Context and Resources (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	Environmental stressors Resources / material resources Organisational culture /climate Salient events / critical incidents

	Person x environment interaction
	Barriers and facilitators
12. Social influences (Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)	Social pressure
	Social norms
	Group conformity
	Social comparisons
	Group norms
	Social support
	Power
	Intergroup conflict
	Alienation
	Group identity
	Modelling
13. Emotion (A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)	Fear
	Anxiety
	Affect
	Stress
	Depression

	Positive / negative affect
	Burn-out
14. Behavioural Regulation	Self-monitoring
(Anything aimed at managing or changing objectively observed or measured actions)	Breaking habit
	Action planning

2.3 Validated questionnaire for using Theoretical Domains Framework in quantitative studies

The Theoretical Domains Framework (TDF) since its inception has been used by research teams across the health domain. For example, researchers in Australia have used it to identify the barriers and enablers to address the issue around acute low back pain (McKenzie et al, 2008; McKenzie et al, 2009) and develop theory-informed behaviour change interventions. In Denmark, it has been used to improve behaviours surrounding the implementation of tobacco use prevention and cessation counselling among dental providers (Amemori et al, 2011). In the UK, examples include research into the barriers and enablers of hand hygiene (Dyson et al, 2010); understanding clinician's blood transfusion behaviour (Francis et al, 2009; Francis, Tinmouth & Stanworth, 2009) and identifying barriers in the implementation of guidelines relating to schizophrenia (Michie et al, 2009). Most of the TDF research has used the exemplar questions developed by (Michie et al, 2004) in interviews and focus group discussions to develop a comprehensive theoretical assessment of the behavioural problem. For a more quantitative exercise using TDF, Huig et al (2014) developed a generic questionnaire in

English to assess the 14 domains of TDF. Some of the items measuring constructs in the TDF were adapted from previously published questionnaires, while some of them were newly developed by the researchers informed by academic literature. The items in the questionnaire were formulated in a generic way so that they can be adapted for use in different health behaviour change contexts. The table in Appendix 3 shows the generic questionnaire developed and validated by Huig et al (2014).

I adapted this generic questionnaire to develop a TDF based questionnaire to identify the barriers and enablers for patients to adhere to their antibiotic medication course. In the next chapter I explain in detail the questionnaire that was developed and findings of the survey results. Most of the studies using TDF have either used the questionnaire to prepare qualitative interviews or where a quantitative survey has been used the sample size has ranged from 40 – 60. TDF is yet to be administered to a large national sample and analysed. This is one gap in existing TDF literature that I tried to fill.

3 CHAPTER 3: National Survey of Pakistani Population to Assess Adherence Rates and TDF

In the last section I explained in detail the Theoretical Domains Framework (TDF) that I selected for going through the 'Theory' stage suggested by the Medical Research Council. In this section, I detail the implementation of the TDF to a national sample of the Pakistani population along with the analysis, results and a discussion.

I was interested in understanding why people fail to adhere to their medication. In this regard, I developed a survey derived from the TDF to obtain reports from patients on their experience taking medication and if and why they failed to complete their treatment.

However, TDF alone is not sufficient to understand the barriers to medication adherence faced by the patients and there is a need to have a dependent variable that measures the extent of adherence among the people interviewed in the national sample. Below, I will first discuss a few common ways used in research to measure the patient's adherence to medication, their pros and cons and finally justification for the selection of measures that I decided to use to supplement the TDF questionnaire. I will then explain in detail the national survey I carried out to measure medication adherence rate of the Pakistani population and the use of TDF to assess people's barriers to taking medication.

3.1 Measuring adherence rate

We have now established that non-adherence to antibiotic medication can have serious impacts not only to the individual but the society as well. A crucial element in developing successful interventions to improve medication adherence is the ability to measure the adherence rates among the patients, that is, its incidence. There has however been a lack of general guidance for researchers in this field to choose the appropriate measures of medication adherence (Lam et al., 2015).

Measuring adherence to medication is quite a challenging task since patients take their pills often in private. Therefore the ability to know objectively whether a patient has taken their pill or not is quite difficult.

Measures of medication adherence can be classified into two types: direct measures and indirect measures.

3.1.1 Direct Measures

Direct measures involve measurement of the medication or its metabolite concentration in the body fluids of the patient. These body fluids can be blood or urine and adherence is measured by observing the presence of a biological marker which is given along with the medication. Furthermore, other direct measures are inclusive of direct observation of the patient taking their medication.

Direct measures are considered to be the most objective measure of medication adherence but there are a few drawbacks which are associated with it:

(i) Direct measures of medication adherence can be intrusive and can cause anxiety among the patients;

(ii) In some instances, traces of the biological marker can be detected in the blood even long after the medication has been stopped thereby raising concerns over the reliability of the observed data. A few examples can be found in the neuroleptic and psychiatric medications;

(iii) Drug-drug and drug-food interactions can affect the accuracy of the data; and

(iv) Direct measures are expensive and often quite difficult to perform since they require a team of technicians and professionals to manage the whole process and carry out the tests (Lam et al., 2015).

3.1.2 Indirect Measures

3.1.2.1 Measures involving Electronic Medication Packaging (EMP) devices

Another way of measuring adherence is the use of EMP devices. They make use of the latest transmission technology and are incorporated into the packaging of the medication. A few common features among these EMP devices are:

(i) Recording of the dosing events and hence storing data on adherence

(ii) Audio-visual reminders to prompt or cue the patients for the next dose

(iii) Digital displays

(iv) Real-time monitoring

(v) Feedback on the patient's adherence levels (Checchi et al., 2014).

The most commonly used EMP device in adherence related research is the Medication Events Monitoring System (MEMS).

3.1.2.1.1 MEMS

MEMS involve placing a microprocessor in the pill box. Whenever a medication is removed from the container, the microprocessor would record the time and date. The assumption here is that if a pill has been removed from the container, then it has been taken by the patient.

The advantage of MEMS is that it helps to understand the pattern of non-adherence. One can argue that MEMS is not completely objective as the researcher would never know whether the pill that was taken out of the container was actually being consumed by the patient or not. However, a strong case can be made in favour, as it would be quite difficult for the patient to deceive the researcher. This is because the patient would need to demonstrate a keen dedication to opening the container and taking out the pill at the same time every day in order to guarantee that the "adherence" pattern is recorded.

A few disadvantages of the EMP devices and MEMS in particular are:

(i) The patient may accidentally open the container sometimes which could possibly lead to overestimation of the adherence rates;

(ii) The presence of MEMS containers serves as a reminder to the patients that they are being observed which has been reported to result in anxiety and stress among the patients; and

(iii) MEMS are quite expensive devices and therefore it is not a feasible option to use them among large sample sizes (each device costs more than a £100).

3.1.2.2 Self-Report

In a recent systematic review, Nguyen et al. (2014) have identified 43 validated self-report adherence scales. Although self-report can be regarded as a lesser objective measure for medication adherence compared to the other measures discussed in the sections above, but their low implementation cost and simplicity to administer make it very feasible for large sample sizes. In fact, self-report is the only feasible way to measure adherence for large samples.

Among self-report measures for medication adherence, the nearest to a gold-standard is the Morisky's Medication Adherence Scale (MMAS) and therefore only this scale will be discussed below (Culiq et al., 2014).

3.1.2.2.1 Morisky's Medication Adherence Scale (MMAS)

MMAS holds an advantageous position over other self-report measures due to its widespread use among patients with different diseases, in different populations and countries. Furthermore, it is the shortest to administer, easiest to score and very suitable for patients in low and middle income countries. MMAS has been validated in the widest range of diseases and among patients with low literacy rates (Culiq et al., 2014).

The MMAS asks the following four dichotomous response category questions to the patients:

English	
	Keeping the antibiotic course in mind:
Q1	Do you ever forget to take your antibiotic medication? (Yes/No)
Q2	Are you careless at times about taking your antibitoic medication? (Yes/No)
Q3	Sometimes, if you feel worse when you take the antibiotics, do you stop taking it? (Yes/No)
Q4	When you feel better, do you sometimes stop taking the antibiotics? (Yes/No)

A “Yes” response on the question scores a 1 and a “No” response on the question scores a 0. For each patient an adherence score is calculated by aggregating their scores on each of the four questions. The patient is then characterized into a Low, Medium or High adherence category by the following rules:

- If the aggregate adherence score is 3 or 4, then the patient is classified in the Low adherence category;
- If the aggregate adherence score is 1 or 2, then the patient is classified in the Medium adherence category; and
- If the aggregate adherence score is 0, then the patient is classified in the High adherence category.

3.1.3 My selection of the measure for medication adherence and its justification

After examining the different measures of medication adherence, I decided to choose MMAS. Below are the reasons for the selection of MMAS:

(i) Administering MMAS is the best compromise between reliability of data and cost effectiveness. I already had an existent relationship with Gallup Pakistan and they agreed to include MMAS questions in their national omnibus.

(ii) MMAS has been validated for use in low and middle income countries. Furthermore, its dichotomous response category questions are easily comprehensible among individuals with low literacy rates (Culiq et al., 2014).

(iii) Using MMAS gave me the opportunity to collect nationally representative data on medication adherence levels from the Pakistani population. The other measures of medication adherence such as Direct measures or MEMS

required huge amounts of resources (time, money and personnel) to administer to a national sample.

(iv) I already had the intention of running lab experiments which would measure adherence directly and thus it provided a cushion to be less strict on the objectivity of the medication adherence measure used in the formative research.

(v) Although not a very strong argument, but the Department of Health was running an RCT on medication adherence at the same time I was carrying out my research and they were using MMAS as their main outcome variable. This lent me a greater confidence to use MMAS in my national survey.

3.2 National Survey to measure medication adherence rate of the Pakistani population and assessing barriers to medication adherence using TDF

As mentioned at the start of this section, the first step in developing behaviour change interventions to address the problem of medication non-adherence is understanding the extent of non-adherence currently present among the population and also the underlying barriers associated with this non-adherence behaviour. The choice of MMAS as a measure for medication adherence among the Pakistani population and the use of TDF as a tool to identifying barriers to medication adherence have already been argued in the sections above.

Below, I detail the methodology, results and the discussion of the national survey that was carried out administering MMAS and TDF to the Pakistani population.

3.2.1 Methodology

This section details the survey instrument used, participant profile and the data preparation methods used. We used the services of Gallup Pakistan to carry out the survey across Pakistan in May 2015 and collect data from a nationally representative sample of Pakistan.

3.2.1.1 Survey Instrument

3.2.1.1.1 TDF questions

A 31-item questionnaire targeting a national sample of the Pakistani population was developed based on the TDF (see Table below). These 31 items measure the 14 domains that have been discussed in Chapter 2. I started with the generic questionnaire developed by Huig et al (2014), and carried out modifications to create a medication adherence specific TDF questionnaire. The questionnaire was reviewed by TDF expert (Professor Ivo Vlaev) and a few minor adjustments were made upon receipt of his feedback. Participants were asked to rate on a 10-point likert scale how strongly they agreed or disagreed with each of the 31 items of the TDF.

3.2.1.1.2 MMAS questions

Additionally, 4-item MMAS was added (see Table below) to not only serve as a dependent variable for our analysis, but also to generate an understanding of the medication adherence rates across different genders, age levels, income levels and urban/rural setting. The 4 items of the MMAS have already been discussed in Section 3.1.2.2.1.

3.2.1.1.3 Demographics

The questionnaire also asked participants about their age and household monthly income. The interviewers took note of participant's gender and whether the participants belonged to an urban or rural setting.

English		
		Keeping the antibiotic course in mind:
	Q1	Do you ever forget to take your antibiotic medication? (Yes/No)
	Q2	Are you careless at times about taking your antibitoic medication? (Yes/No)
	Q3	Sometimes, if you feel worse when you take the antibiotics, do you stop taking it? (Yes/No)
	Q4	When you feel better, do you sometimes stop taking the antibiotics? (Yes/No)
Completing the antibiotic course means taking all the medication which has been prescribed to you and not stopping in the middle.		
On a scale of 1 - 10, how strongly do you agree/disagree with the following statements with 1 being strongly disagree and 10 being strongly agree:		
Knowledge	D1.1	I know that antibiotic medication course should be finished
	D1.2	I know how to complete the antibiotic medication course
Skills	D2.1	I have the skills to complete the antibiotic medication course
Social/professional role and identity	D3.1	It is my responsibility as a patient to complete the antibiotic medication course
Beliefs about capabilities	D4.1	I am confident that I can complete the antibiotic medication course even if I am not motivated
	D4.2	I am confident that if I wanted I could complete the antibiotic medication course
	D4.3	For me, it is difficult to complete the antibiotic medication course
Optimism	D5.1	With regards to completing the antibiotic medication course, nothing bad will happen
	D5.2	With regards to completing the antibiotic medication course, if something can go wrong it will
Beliefs about own consequences	D6.1	For me, completing the antibiotic medication course is useless
	D6.2	If I complete the antibiotic medication course. It will benefit me
Reinforcement	D7.1	Whenever I complete the antibiotic medication course, I feel recognition from people who are important to me
	D7.2	Whenever I complete the antibiotic medication course, I get rewarded
Intentions	D8.1	I intend to complete the antibiotic medication course next time
Goals	D9.1	I have a clear plan of how I will complete the antibiotic medication course
	D9.2	For me covering something else on my agenda is often a higher priority than completing the antibiotic medication course
Memory, attention and decision processes	D10.1	For me completing the antibiotic medication course is easy to remember
	D10.2	I often forget to complete the antibiotic medication course
	D10.3	I get distracted from completing the antibiotic medication course
Environmental context and resources	D11.1	In my society, completing the antibiotic medication course is common
	D11.2	Within the socio-political context there is good communication between myslelf and my doctor
	D11.3	Prior to giving the prescription, doctor advised me to complete the antibiotic medication course
Social influences	D12.1	My friends and family are helpful in my completion of the antibiotic medication course
	D12.2	Most people who are important to me think that I should complete the antibiotic medication course
	D12.3	People I know complete their antibiotic medication course
Emotion	D13.1	I generally feel worried or concerned about not completing the antibiotic medication course
	D13.2	I generally feel good about completing the antibiotic medication course
	D13.3	I generally enjoy my normal day to day activities
	D13.4	I generally feel unhappy and depressed
Behavioural regulation	D14.1	I usually complete my antibiotic medication course without thinking
	D14.2	I keep track of my progress in completing the antibiotic medication course

3.2.1.2 Participants

All interviews were conducted face-to-face and in Urdu (the national language of Pakistan). Gallup Pakistan provided assistance in the translation of questionnaire from English to Urdu. Gallup Pakistan provided the respective weightings to make the data nationally representative. It is to be noted that the weightings were on the provinces and whether the area is Urban or Rural. For the purpose of analysis within this section, we will only be looking at national figures and therefore the weightings can be applied.

Gallup Pakistan has a national panel which they use for their weekly omnibus and our survey was administered to this national panel. A total of 1,892 men and women (all above the age of 18) across Pakistan were surveyed. This included 1010 males and 882 females. The survey was carried out from 18th-19th May 2015.

3.2.1.3 Data preparation

In this section I briefly describe how the data was prepared following its collection by Gallup Pakistan's interviewers. These are standard practices at Gallup Pakistan.

3.2.1.3.1 Field Edit or Intake Edit

At least 30% of each interviewer's interviews were visually checked by the field supervisor before passing them to Data Coding/Entry department. Any problems or missing information identified during this field edit were explained to the relevant interviewer and they were instructed to rectify them either through telephone and/or revisit to the respondent for clarification and re-asking the missing questions.

3.2.1.3.2 Supervision & Back Checking

The field supervisor carried out at least 20% back checking on the work completed by each interviewer to ensure authenticity of data. This was done by either visiting or calling the respondents and confirming some of the answers that the respondents gave.

3.2.1.3.3 Data coding and entry

The questionnaires received from the field were checked. A coding scheme was prepared on the basis of the questionnaire and the data was entered in SPSS. 20% of the data was double punched and a verification exercise was carried out to ensure that correct data has been entered.

3.2.1.3.4 Data cleaning

After completion of data entries and double punch, all data was cleaned by using a data-cleaning program written in SPSS. Gallup Pakistan uses its own proprietary software, the "Hunter" program to track interviewer performance by searching for patterns and duplicates in the data over time. The Programme searches for patterns and duplicates that may indicate that an interview was not properly conducted by an interviewer. The Hunter program includes three primary tests:

- Equality test – compares interviews for similarities, grouped by interviewer, within sampling point, province, or any other variable. Interviews with an interviewer average of 95% or higher equality are flagged for further investigation.
- "Don't Know" / "Refused" (that is, non-response) test – determines the percentage of nonresponse for each interviewer's cases. Interviewers with 40% or higher nonresponse are flagged for further investigation.

- Duplicates test – compares cases across all interviewers and respondents to check for similarity rates. This test will flag any pair of interviews that are similar to each other. Typically, any cases that have a similarity of 95% or higher are flagged for further investigation.

Any interview that did not pass one of the Hunter tests was pulled out for additional screening. If the interview did not pass screening, it was removed from the final database before delivery. Furthermore, Gallup Pakistan carried out additional checks to evaluate the interviewer's work as a whole.

Interviewers' performance was judged on the basis of four statistical tests. These tests took variance and non-response into account by interviewer. Three of these tests highlighted potential problems, and one attempted to explain them. Below is a brief description of the tests:

Test 1 looked for patterns of consistent responses across questions by a respondent. This typically occurs in rating batteries, with the respondent giving the same answer (such as "agree somewhat") to every item in the battery, despite random or rotating reading order. This was more of a concern in our study as we were asking respondents to give ratings of agreeability to 31 statements.

Test 2 looked for patterns of consistent responses across respondents within an interviewer's pool of respondents. While it is possible that an interviewer with fifteen to twenty respondents might legitimately have all of them answering identically to a number of questions, it suggests there can potentially be a problem. Of course, a poorly designed question or a highly skewed public agenda may produce a respondent pool

with zero variance for one or more questions, but an interviewer who had much less variance in responses across his or her interview pool compared to peers was flagged for further investigation.

Test 3 looked for patterns of non-response and sought to identify interviewers who had substantially higher average rates of non-response across their interviewer pools compared to their peers. A high rate across the board may indicate a poorly designed questionnaire (too sensitive, too difficult) or poor timing – such as the survey being conducted at a time when people are distracted (for example, an important holiday like Eid or Ramadan) or when certain questions are too sensitive (such as in the run-up to an election). However, statistically significant higher rate of non-responses compared to an interviewer's peers were flagged for further investigation.

Finally, Test 4 for interviewer productivity was used both as a test and a diagnostic. While field managers want productive interviewers, Gallup Pakistan tends to question those who are too productive. They looked at two indicators: average length of interview and number of completed interviews per interviewing day. Interviewers whose interviews were much shorter than the average or who complete many more interviews per day (generally measured in terms of one or two standard deviations above the norm) were singled out for management attention. These productivity measures may also explain other problems, in whole or in part. Interviewers who are moving too fast through the questionnaire may stimulate patterned responding, or they may start skipping responses and coding the results themselves.

3.3 Analysis

Once the clean data was received, standard descriptive statistical analysis was carried out to assess the incidence of adherence to antibiotic medication using the MMAS-4 categorisation (the mechanism of creating the Low/Medium/High adherence categories has already been mentioned in Section 3.1.2.2.1). Furthermore, a behaviour change scorecard was developed through the aggregation of TDF statements to get scores for each of the 14 domains of TDF.

To test for differences in each of the 14 domains on some key variables (e.g. age, monthly household income, gender etc.), one-way ANOVA was used.

To test for associations between the 14 domains, pearson correlations were analysed. In line with previous research, correlation coefficient values between 0.00 and 0.30 were considered as negligible, values between 0.31 and 0.50 as weak, values between 0.51 and 0.70 as moderate and values between greater than 0.70 as strong (Huig et al, 2014).

In order to identify the barriers to medication adherence, ordinal logistic regression was used to examine the relationship between the 14 domains of the TDF (independent variables) and the MMAS adherence category (dependent variable) (Scott et al., 1997). Ordinal regression was used because the number of response categories for the dependent variable exceeded two.

Some of the TDF statements are framed negatively, for example: “I often forget to complete the antibiotic medication course” and a higher agreeability score on this statement means that forgetfulness is a barrier. Since the general understanding of the aggregated scores is that a lower score corresponds to that particular domain as a

barrier, therefore the responses of participants for the statements that were framed negatively (like the forgetfulness one just mentioned) were reverse coded before being aggregated with other statements to make up the score for that particular domain.

Ordinal regression is based on proportional odds assumption, that is, that the odds of a unit increase in the dependent variable are the same across the different response categories (Scott et al., 1997). This means that the odds of a person being in the "Medium" or "High" MMAS adherence categories compared to the "Low" MMAS adherence category is assumed to be the same as the odds of a person being in the "High" MMAS adherence category compared to the "Medium" or "Low" MMAS adherence categories. A non-significant test result (parallel lines test in SPSS) verifies the proportional odds assumption.

The approach to the analysis was exploratory in nature and statistical analysis was performed using SPSS version 19.

3.4 Results

The survey was administered to a national sample of 1,892 people. Of these, 682 (36%) passed through the screening question of whether they have taken an antibiotic or not. The data from these 682 people was analysed.

I described the respondents along with their demographics in the table below. The mean age of the participants was 35 years (SD=10, range 18 to 76 years). There was a fairly equal mix of gender in the final sample with 395 (58%) men and 287 (42%) women. The majority of the people were based in a Rural setting (64%) and had a monthly household income of less than Rs. 30,000 (approx. £200).

Age of the Respondent	Percent
Under 30	34.3
30 – 50	57.4
50+	8.3

Gender	Percent
Male	57.8
Female	42.2

Location	Percent
Urban	36.1
Rural	63.9

Monthly HH Income	Percent
Up to Rs. 7000	14.7
Rs.7001-Rs.15000	30.5
Rs.15001-Rs.30000	29.1
More than Rs.30000	10.9

Below is the percentage of people who responded “Yes” to each of the MMAS questions:

MMAS - 4

60% Do you ever forget to take your antibiotic medication when you were completing the antibiotic course?

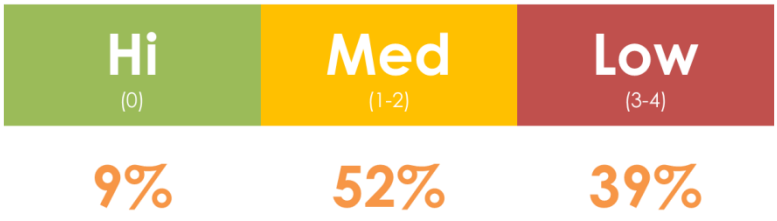
50% Are you careless at times about taking your antibitoic medication?

56% Sometimes, if you feel worse when you take the antibiotics, then do you stop taking it or not?

39% When you feel better, do you sometimes stop taking the antibiotics or not?

After aggregating the scores of the participants based on the method described in Section 3.1.2.1, below is the distribution of the participants among the “High”, “Medium” and “Low” categories of the MMAS.

MMAS - 4



There were a few non-responses in the TDF statements and data relating to the TDF statements was only analysed from the sample of respondents (N=549) who responded to all the questions.

The table below shows the means and standard deviations for all the 14 domains of the TDF. Reinforcement and Optimism have scored considerably low compared to the rest of the domains.

	TDF Domain	Mean	Std. Dev.
CAPABILITY	Knowledge	6.55	2.83
CAPABILITY	Skills	6.22	2.57
CAPABILITY	Memory, attention and decision processes	5.90	1.71
CAPABILITY	Behavioural regulation	5.84	2.21
OPPORTUNITY	Social influences	6.10	2.23
OPPORTUNITY	Environmental context and resources	6.23	2.18
MOTIVATION	Reinforcement	5.18	2.09
MOTIVATION	Emotion	6.27	1.71
MOTIVATION	Social/professional role and identity	6.87	2.73
MOTIVATION	Beliefs about capabilities	6.28	1.60
MOTIVATION	Optimism	5.17	1.75
MOTIVATION	Intentions	6.09	2.91
MOTIVATION	Goals	5.81	1.65
MOTIVATION	Beliefs about consequences	6.57	2.03

The cross-tabulation below shows how scores on each of the 14 domains varied across the three MMAS medication adherence categories. Generally, as you move from "Low" to "High" adherence category the scores in each of the 14 domains increase.

		MMAS Adherence Categories (Mean)		
	TDF Domain	**Low**	**Med**	**High**
CAPABILITY	Knowledge	6.20	6.70	7.30
	Skills	6.00	6.00	7.00
	Memory, attention and decision processes	5.47	6.05	6.92
	Behavioural regulation	5.70	5.80	6.40
OPPORTUNITY	Social influences	6.00	6.24	5.79
	Environmental context and resources	6.04	6.33	6.46
MOTIVATION	Reinforcement	5.20	5.20	5.20
	Emotion	6.01	6.42	6.59
	Social/professional role and identity	7.00	7.00	7.00
	Beliefs about capabilities	6.10	6.30	6.94
	Optimism	5.20	5.10	5.50
	Intentions	6.00	6.00	7.00
	Goals	5.60	5.90	6.10
	Beliefs about consequences	6.10	6.80	7.20

The table below shows the correlation matrix of the 14 domainns. Strong positive correlations were found between Knowledge and Intention (r=0.71, p<0.0001), and 'Enviromental context and resources' and 'Social Influences' (r=0.74, p<0.0001). Moderate positive associations were found in 17 out of 91 domain pairs. The domains Memory, Attention and Decision Processes, Reinforcement, Optimism and Goals had weak or negligible associations with any other domain.

	Knowledge	Skills	Social/professional role and identity	Beliefs about capabilities	Optimism	Beliefs about consequences	Reinforcement	Intentions	Goals	Memory, attention and decision processes	Environmental context and resources	Social influences	Emotion	Behavioural regulation
Knowledge	1.00	0.65	0.65	0.51	-0.12	0.51	0.32	0.71	0.29	0.10	0.69	0.66	0.65	0.63
Skills		1.00	0.54	0.40	-0.09	0.43	0.35	0.57	0.24	0.15	0.56	0.53	0.52	0.48
Social/professional role and identity			1.00	0.54	-0.11	0.51	0.24	0.62	0.22	0.12	0.59	0.57	0.60	0.49
Beliefs about capabilities				1.00	-0.12	0.48	0.16	0.52	0.23	0.19	0.43	0.45	0.50	0.34
Optimism					1.00	-0.23	0.01	-0.11	0.00	0.00	-0.18	-0.24	-0.21	0.04
Beliefs about consequences						1.00	0.03	0.44	0.29	0.26	0.44	0.44	0.54	0.27
Reinforcement							1.00	0.35	0.12	-0.15	0.41	0.46	0.25	0.36
Intentions								1.00	0.32	0.12	0.64	0.66	0.64	0.55
Goals									1.00	0.32	0.23	0.21	0.30	0.17
Memory, attention and decision processes										1.00	0.00	0.02	0.14	-0.06

Environmental context and resources											1.00	0.74	0.66	0.60
Social influences												1.00	0.63	0.57
Emotion													1.00	0.50
Behavioural regulation														1.00

Ordinal regression was used to investigate the association between the 14 TDF domains (independent variable) and the three MMAS adherence categories (dependent variable). Together the 14 domains accounted for a significant amount of variance in the outcome, $\chi^2(14)=74.659$, $p<0.0001$. Skills ($b=0.158$, $SE=0.048$, $OR=1.17$, $p=0.001$); Beliefs about Consequences ($b=0.143$, $SE=0.057$, $OR=1.15$, $p=0.013$); Memory, Attentions and Decision Processes ($b=0.24$, $SE=0.058$, $OR=1.27$, $p<0.0001$) and Social Influence ($b=-0.152$, $SE=0.067$, $OR=0.86$, $p=0.024$) were significantly associated with the MMAS adherence categories. Overall the model accounted for about 15.1% of the variance in the outcome, Nagelkerke pseudo $R^2=0.151$. The proportional odds assumption was verified using the Test of Parallel Lines, $\chi^2(14)=15.297$, $p=0.358$. The Goodness of Fit statistics confirm that the model fits well, Pearson $\chi^2(1076)= 1101.408$, $p=0.288$ and Deviance $\chi^2(1076)= 936.011$, $p=0.999$.

3.5 Discussion

Only 36% of the people interviewed said that they had taken an antibiotic in the past. This statistic does raise a concern as one would expect that at least the majority of the people would have taken an antibiotic once. Upon reflection, it has been surmised that it might be that some people are not familiar with the term ‘antibiotic’ but have in reality

gone through the medication course. Given that many people might not be aware that the medication prescribed to them is an antibiotic; there is a greater chance that they would be unaware of the fact that they should be completing their course and what might be the possible consequences of non-adherence. There is clearly a need to raise more awareness around this issue among the population.

39% of those who recognised they had taken an antibiotic were in the “Low” adherence category of MMAS, and 52% were in the “Medium” adherence category. It is known that many behavioural factors are at play contributing to such low adherence rates among the people and hence there is a very strong case to develop theoretically informed behaviour change interventions.

60% of the people admit that they often forget to take their pills. This directly feeds into the strong need to address the issue of forgetfulness when developing interventions to improve adherence to antibiotic medication. Furthermore, “Memory, Attention and Decision Processes” was found to have a significant relationship with adherence. It is quite natural for people to forget about taking their medication. This can especially be the case in situations where a person does not experience any symptoms of the disease. As the symptoms go away and the person is feeling better, he or she often gets distracted by their work, family and other social factors and simply forgets to take their medication.

39% of people admit that when they feel better they sometimes stop taking the antibiotics cementing our initial suggestion that ‘feeling ok’ is one of the factors associated with partial adherence to antibiotics. This argument is further strengthened by a low score in the domain of “Reinforcement” in the TDF scorecard. Once the

symptoms go away and patients are feeling better there is not really much incentive for them to continue taking their pills.

The high score in “Beliefs about Consequences” and the low score in “Optimism” reveal a very interesting story: patients believe strongly that taking antibiotics is useful and beneficial to get rid of the disease but they also simultaneously believe that taking medication can cause unintended harm as well (such as its side effects and it being unnatural or non-organic). Therefore it seems that the rationale adopted by the patients is to take the medication as long as required, that is to take the medication as long as one is feeling sick and stop as soon as one feels better.

It can be concluded from the correlation matrix that the 14 domains are not all independent of each other. However, the Theoretical Domains Framework does not assume independence of domains any way. It is reasonable to expect associations between some of the domains. For instance, an intention to complete the medication course next time would strongly depend on the patient knowing that the course should be completed. Similarly, it was found that ‘Environmental context and resources’ and ‘Social Influences’ are strongly correlated. Both these domains form the ‘Opportunity’ part of COM-B model where both physical and social opportunity needs to be present for the patient to complete their medication course. This is being validated by the high correlation scores between the two domains. Memory, Attention and Decision process was found to have negligible association with all the domains except Goals where weak positive association was found. This domain relates to the fast system 1 thinking (reference to kahneman book here) and therefore is almost independent of the slow system 2 thinking rest of the domains. One of the items in Goals asked participants

about higher priorities on agenda than taking the medication which can also create a distraction and make patients forget, hence the weak association found between the two domains.

“Beliefs about Consequences” had a significant relationship with people’s adherence to antibiotic medication. The stronger the belief among people that completing an antibiotic medication will benefit them and improve their health outcome the greater is the likelihood of them having a higher adherence rate. This domain falls generally under the motivational aspect of behaviour. A greater belief in positive consequences of a particular behaviour increases the motivation of the person to perform that behaviour. The finding here seems to suggest that any behaviour change intervention developed to address the problem of non-adherence to antibiotic medication should include elements that enhances a person’s belief about the positive consequences of completing an antibiotic medication course and perhaps also negative consequences of not completing the course.

“Memory, Attention and Decision Processes” also had a significant relationship with people’s adherence rate to antibiotic medication. It is quite easy for people to forget taking their medication and often there are other things on their agenda that distract them from this action. This domain falls generally under the psychological capability aspect of behaviour. In order for a person to perform behaviour, he/she needs to have the psychological capability necessary for performing that particular behaviour. The finding here seems to suggest that even though people want to take their medication, they often find it difficult to do so. These results hint towards including some form of

reminder mechanism in the development of any behaviour change intervention that is addressing the issue of non-adherence to antibiotic medication.

The third domain that had a significant relationship with people's adherence to antibiotic medication was "Social Influence". However, the data shows a negative relationship between social influence and adherence rate. This result is slightly confusing as essentially it means that the more social influence there is for people to take their antibiotics the lesser is the likelihood of taking their medication. This finding seems to be counterintuitive but it does point to a need to carry out further analysis and look for any interaction effects that might be at play.

It is quite interesting to note that "Reinforcement" scored considerably low compared to the rest of the domains in the TDF scorecard but the ordinal regression did not reveal "Reinforcement" to be a significant domain in predicting the MMAS adherence categories. It can be seen from the TDF scorecard that "Reinforcement" scored low in all three MMAS adherence categories. Essentially, once the symptoms go away and patients are feeling "all ok" there is not a lot of incentive for them to carry on taking their pills. This experience of symptoms going away earlier than the elimination of the disease is a very important and consistent phenomenon faced by patients with bacterial infections. Since this phenomenon is an inherent feature of the disease, patients do not have any control over it and hence we see low scores on "Reinforcement" among all three MMAS adherence categories rather than this domain affecting each of the three MMAS adherence categories differently.

Although the results from this national study are very interesting and we are able to carry out a theoretically-informed behavioural diagnosis of the non-adherence problem,

we were only able to use 36% of the data (since the rest didn't pass through the screening question). As we have discussed, it is very likely that more people have taken an antibiotic medication but do not recognize the name. One of the learning outcomes from this study has been a more detailed understanding of the local terminology that doctors and patients use for "antibiotic medication". This terminology should then be used in the design of questions for any subsequent antibiotic medication related surveys. People were asked to recall if they have ever taken an antibiotic medication course and did not limit ourselves to screening people who have only recently been prescribed an antibiotic medication. There is a potential issue that some people might misremember their experience and it will be better to screen only recent patients for the next study.

4 CHAPTER 4: What do patients learn from their doctors?

Moving on from the Theory stage, my next step was to develop a model that captures the non-adherence behaviour of the patients who have been prescribed antibiotic medication. In this Chapter I discuss the formative research that I carried out to understand the experience that patients goes through from when they get sick until the end of the medication course. In Chapter 5, I then describe in detail the model that I used and the results of the modelling experiments.

For my formative research, I carried out a national survey of the Pakistani population to understand the communication that takes place between the doctor and the patient at the time of prescribing a medicine. I further shadowed a GP in Pakistan to understand the context and gain first-hand experience of the doctor-patient communication. I further interviewed a few GPs to gain understanding of the common antibiotic prescriptions such as dosage and duration to help me develop the best analogue in my experimental game model.

My motivation to carry out a formative research was to use the results of the formative research to develop the communication that I would carry out with the participants on my lab experiments in the modelling stage.

4.1 National Survey of Pakistani Population to understand the Doctor-Patient communication at the time of prescription

An important element in modelling the act of pill taking and the observed non-adherence behaviour is to track the whole patient cycle from the time the patient sees

the doctor, to the time when antibiotic medication is prescribed and the patient is taking the pills at the required intervals daily.

In this regard it is important to understand the communication that takes place between the patient and the doctor at the time of antibiotic prescription. Due to ethical and confidentiality concerns it is quite difficult to find data on the exact communication that takes place between the GP and the patient at the time of prescription.

Gallup Pakistan carries out a weekly national survey and I decided to add a few questions to their omnibus regarding doctor-patient communication. These questions were asked to the people who had visited a GP in the past 2 months and had medication prescribed to them. Of course, using recall to understand the doctor-patient communication is not ideal but this was the best option that I had. However, given that I was able to administer my survey to a national sample it added a lot more weight to the findings.

4.1.1 Methodology

This section details the survey instrument used, participant profile and the data preparation methods used. Gallup Pakistan carried out the survey on a nationally representative sample across Pakistan in April 2016.

4.1.1.1 Survey Instrument

The questionnaire was based on the National Institute for Health and Care Excellence (NICE) guidelines on effective antimicrobial medicine use and the global study carried out by Worldwide Independent Network of Market Research (WIN) on Doctor-Patient communication. I used the NICE guidelines as a substitute because I was not able to

find a similar guideline in the Pakistani health system. There was a screening question at the start to determine whether the interviewee had been to a doctor in the last 2 months or not. People were then asked about the diagnosis that the doctor provided. The questionnaire was split into two main sections.

The first section asked people yes/no questions about whether the doctor told them which medicine to take, how often to take, how to long to take and other such questions. Essentially, the first section was inspired by the NICE guidelines regarding what should be communicated to the patient at the time of antibiotic prescription. I used these guidelines to create a yes/no checklist which constituted the first section of the survey.

The second section was inspired by the global study carried out by WIN on Doctor-patient communication. This section included questions that related more to the doctor's behaviour, the overall experience of the patient and the trust and confidence that the patient had in the doctor that he/she visited.

The complete questionnaire can be found in Appendix 2. It is to be noted that the actual questionnaire was in Urdu and Appendix 2 shows the translated version of the actual questionnaire in English.

4.1.1.2 Participants

All interviews were conducted face-to-face and in Urdu (the national language of Pakistan). Gallup Pakistan provided assistance in the translation of questionnaire from English to Urdu. Gallup Pakistan provided the respective weightings to make the data nationally representative. It is to be noted that the weightings were on the provinces and

whether the area is Urban or Rural. For the purpose of analysis within this section, we are only looking at national figures and hence the weightings can be applied.

Gallup Pakistan has a national panel that they use for their weekly omnibus and our survey was administered to this national panel. A total of 1,686 men and women across Pakistan were surveyed. This included 907 males and 760 females (with 20 participants whose gender was not specified). The survey was carried out from 24th-30th April 2016.

4.1.1.3 Data preparation

The data was collected, cleaned and coded in the same manner as has been described in Section 3.2.

4.1.2 Analysis

The main purpose of carrying out this national survey was to understand the exact communication between the doctor and the patient at the time of medication prescription. My motivation behind this endeavour was to use the results of this survey to develop the communication that I would carry out with the participants on my lab experiments in the modelling stage. Standard statistical descriptives were thus sufficient for my purpose and hence descriptive statistical analysis was carried out.

4.1.3 Results and Discussion

The survey was administered to a national sample of 1,686 people. Of these, 431 (26%) passed through the screening question of whether they have been to a doctor in the past 2 months or not. The data from these 431 people was analysed.

The mean age of the participants was 35 years (SD=11, range 18 to 76 years). There were slightly more males than females in the final sample with 241 (56%) men and 190 (44%)

women. Majority of the people were based in a Rural setting (64%) and have a monthly Household income of less than Rs. 30,000 (approx. £200).

The top three diagnosis of the doctor were Fever (42%), Blood Pressure (15%) and Influenza (12%) commonly regarded as Flu. The question regarding the diagnosis was an open ended question and the responses were subsequently coded. The question asked to the people was “What did the doctor diagnose? What did the doctor tell you about your health problem?” and it is very interesting to note that the top three responses all are symptoms rather than the disease itself. For example, a person might have had fever because he/she had a bacterial infection, or a person might have had flu because he/she had a viral infection. In this case, the diagnosis would have been a bacterial or viral infection rather than fever or flu. In fact most of the responses to this open ended question were symptoms rather than actual disease. There can be different reasons for this result. It might be that the doctors did not communicate the correct diagnosis to the patients, or the patients forgot what the doctor told them about their diagnosis and remembered the reason why they went to see the doctor at the first instance. It is also possible that the people surveyed misunderstood the question and instead replied to a different question that is “What was wrong with your health?” In any case, there seems to be quite a fuzzy discrimination between disease and symptoms during the doctor-patient communication and even after in the mind of the patient. If doctors have been informing patients that they have fever or flu etc. as their diagnosis then in patient’s mind the symptoms become the disease and one can see why many people would stop taking their medication once the symptoms are gone and they would incorrectly assume that the disease is gone. If doctors have been informing patients the

correct diagnosis but instead patients have been replacing the disease with symptoms in their minds then again it creates the same problem. Further work definitely needs to be done to investigate how disease and symptoms are discriminated in the minds of the doctors and the patients and how it can be communicated effectively.

Following the diagnosis question people were asked a battery of yes/no questions based on the NICE guidelines on what should be communicated by the doctor to the patient. 94% of the people said that the doctor told them what medicine to take. One explanation for the rest 6% who weren't told what medicine to take might be that they weren't prescribed any medication. 84% of the people said that the doctor told them how often to take the medication. 82% of the people said that the doctor told them how long to take the medication for. 67% of the people said that the doctor told them about the consequences of not completing the medication course which means that quite a few patients (one-third) were unaware of the importance of finishing a medication course. 65% of the people said that the doctor discussed the benefits and the harms of the medicine while 62% said that they were informed by their doctors what they should do if their condition deteriorates. 73% of the people said that their doctor told them that they should complete their medication course and not leave it half way through. This means that in some cases a doctor might inform the patient that they should complete the medication course but not give the patient a reason for why they should be doing so.

The people were then asked to rate some other features of their visit to the doctor. The table below shows that people were generally quite satisfied with how the doctor interacted with them.

	Very good (%)	Good (%)	Neither good nor poor (%)	Poor (%)	Very poor (%)
Giving you enough time	43	44	7	3	1
Listening to you	33	50	9	5	0
Explaining tests and treatments	35	40	17	5	0
Involving you in decisions about your care	30	50	12	4	0
Treating you with care and concern	33	43	14	5	2

65% of the people said that they had complete confidence and trust in the doctor whom they visited, while 39% of the people had confidence and trust to some extent in the doctor whom they visited. Generally, people placed quite a lot of trust and confidence in their doctors.

4.1.4 Conclusion

Although the results of the survey were very helpful in clearly identifying the pieces of information that gets communicated to the patient at the time of prescription, but it should be noted that the survey looked at patient-doctor communication at the time of prescription of any medicine which of course included antibiotic medication but also included prescription for other illnesses. Looking at the top three diagnoses that patients identified it seems that prescription of an antibiotic would have been quite common; however this cannot be affirmed conclusively. I avoided asking people whether an antibiotic was prescribed or not because I learnt from my previous survey

(discussed in Chapter 3) that many people did not comprehend the word “antibiotic”. I pondered over the possibility of taking a snapshot of the prescription and then coding it to identify whether an antibiotic was prescribed or not. However, upon consultation with colleagues at Gallup this exercise was not practical both in terms of feasibility (since people were screened on whether they visited a doctor in the last 2 months there was a great chance that they would have misplaced their prescription) and cost (transcribing the prescription and getting them vetted by a pharmacist to determine whether antibiotic was prescribed or not would have required a lot more resources from Gallup which would have required funding beyond the budget that was available to me).

It is reasonable to conclude from the results in Section 4.1.3 that in most instances the following gets communicated by the doctor to the patient at the time of medication prescription:

- Which medicine to take
- How often to take the medication
- How long the medication should be taken
- The consequences of not completing the medication course
- That the medication course must be completed and not left half way through

In order to ensure that I have a good analogue for the modelling stage, I had to make sure the above pieces of information were communicated to the participants of my lab experiment. Section 5.9 explains in details how an analogue was created in the modelling stage for each of these points mentioned above.

4.2 Shadowing a GP

In order to gain a deeper understanding of the patient's experience with the doctor I decided to shadow a GP in Islamabad (capital city of Pakistan) for two days in his private practice in the evening. I carried out this qualitative exercise while the national survey was being conducted by Gallup. I was interested in directly observing the interaction partly to develop a richer understanding of the context and partly to later relate my experience with the results of the national survey. The required permissions were taken prior to my shadowing exercise. My two visits to shadow the GP were on 28th and 29th April 2016. Below I describe my observations during the two days.

- On average, the GP spent 10 minutes with each patient.
- To each patient he would first ask them about their health problem, that is, the reason for their visit. Some of the patients were not able to clearly state their symptoms, while some did not fully state their symptoms. In these instances the GP would prompt the patients to get a better understanding of the problem. I found patients to be quite comfortable in communicating to the GP what health problem they have been experiencing.
- There were quite a lot of return patients. These were the people who came last week, received a prescription from the GP and were advised to return after a week for evaluation of the progress.
- Two patients were prescribed with an antibiotic medication. The GP communicated very clearly to the patients when to take the pill (he suggested to take the pills with their meal times) and how long to take the pills for (he gave medication for 5 days). However, the GP did not mention to the patients that they

should complete the full duration of the medication course, nor did he mention the consequences of not completing the medication course. Upon receiving the prescription, the majority of the patients enquired from the GP whether there were any other precautions that they should take such as avoiding eating at certain items or other such issues.

4.3 Conclusion

The formative research that I carried out helped me to understand the doctor-patient interaction very clearly. Although in my qualitative exercise (shadowing the GP) I found that the GP did not completely adhere to the standard guidelines on what should be communicated to the patient but the results of the national survey do reveal that generally the doctors do tick all the boxes of the guideline. There definitely exists an opportunity to improve the doctor's communication to the patient to include delivering information about the importance of completing the antibiotic medication course and the consequences of non-adherence. However, it is also interesting to note that the majority of the people who were surveyed did possess the knowledge that the medication course should be completed and not left half way through. However, we have seen in the results in Chapter 3 that non-adherence is very high in the Pakistani population. It has been the mantra of behavioural scientists that knowledge or information alone does not induce behaviour change, and hence the need to follow the intervention development cycle suggested by the Medical Research Council.

5 Chapter 5: Modelling stage

It is quite common in the field of behavioural science and economics to model real-life behaviours in a lab setting in an attempt to bottle the phenomenon that the researcher is interested in investigating. However, introducing this modelling approach in the development of complex interventions is often not found in the health behaviour change literature (Michie et al., 2005). In most instances, researchers have some intuitions on what might work or borrow an idea which worked somewhere else and go straight into running an RCT. We have already discussed in Section 1.2.6 and 1.2.7 how this approach might not be the most effective and the suggestions given by the Medical Research Council on following the Theory-Modelling-RCT process. In this section, I first highlight a few advantages of using the modelling approach along with an example in the literature which influenced my thoughts on developing my experiment to model the non-adherence behaviour. I will then explain in detail the experiment that I developed to model the non-adherence behaviour of patients in a lab setting. This will include the design of the experiment, its methodology, results and finally a discussion on the outcomes.

5.1 Why modelling

5.1.1 It is cheap

Carrying out research that provides the best value for money is an increasing demand from funders. Running RCTs requires a considerable amount of financial resources and therefore it is quite important that the choice of intervention that is being selected in an RCT is well informed. Using lab experiments to first model the behaviour can provide

important information about the choice and design of the intervention to be tested in an RCT. It is comparatively quite cheap to run a lab experiment and hence modelling through a lab experiment first provides a good value for money when developing behaviour change interventions.

5.1.2 It is quick

Running a multi-arm RCT takes a considerably long time, hence making it even more crucial that the choice and design of the intervention is well informed. Lab experiments can be run fairly quickly providing an opportunity to fine tune and develop an intervention ready for an RCT.

5.1.3 It is much easier on ethics

Obtaining ethics approvals for carrying out any piece of research with patients is quite a lengthy process and fairly strict boundaries are set for what can and cannot be tested. Carrying out lab experiments that model the behaviour that we are interested in can provide a very good opportunity to establish proof of concept before the ethics approval board. Since the lab experiments involve modelling the behaviour in an abstract manner, on most occasions neither does the direct subject need to be mentioned in the experiment nor is the use of patients as participants necessary.

5.1.4 One can answer many what if questions and then take the most successful interventions in the field

Since running RCTs requires considerable financial, time and personnel resources it is often not possible to run more than two or three arms of the trial. A modelling stage prior to running an RCT allows answering many what-if questions that come in the mind of the researcher. A lab setting provides the possibility of running more treatment

groups as compared to in an RCT since lab experiments are much cheaper and quicker to run. Carrying out the modelling stage through controlled lab experiments hence provides a platform for the researcher to explore a variety of interventions that have been theoretically informed, identify what really works and then take the most successful interventions out in the field to be tested in an RCT. If an intervention does not work in the lab setting then it will most likely not work in the real setting as well, however if there is evidence of an intervention being successful in the lab setting then one can make a stronger case of replicating the same intervention in the field and carry out an RCT. Of course lab is a very pure setting and one would always expect the results in the field to be a little more diluted than what is observed in the lab.

5.1.5 Allows identification of exact mechanisms bringing about behaviour change

The Medical Research Council encourages the use of modelling because it allows investigating and identifying the exact mechanisms that are bringing about the behaviour change. Lab experiments take place in a controlled environment and allow the researcher to study isolated effects of the different interventions. This enables a researcher to understand precisely the factors influencing behaviour change. Modelling thus allows the researcher to bottle the phenomenon and create knowledge about the underlying mechanisms of behaviour change that are quite difficult to study through an RCT.

5.1.6 Learning transferable to similar domains

Abstract model also lends its learning to other domains where a similar phenomenon is observed. For example the behaviour of non-adherence to antibiotics can be generalized

to a situation where people respond by behaving in a certain manner as long as the cue or prompt is present in the environment and even though they are supposed to keep performing that behaviour but stop once the cue or prompt is gone.

5.1.7 Allows for testing interventions that are not possible to test in an RCT

In the development of a behaviour change intervention, a researcher might be interested in investigating the effects of various factors or interventions that are not quite straightforward to test in an RCT. Modelling allows for manipulations that cannot be reliably or systematically manipulated in the real setting. For example, I was interested in understanding the relationship between the length of time that symptoms exist and the medication adherence rates of the patients. It has been observed and even accepted by many people that they stop taking their medication once they feel better, that is, once the symptoms are gone (Section 3.4 discusses this in detail). Ideally, I would like to have a few treatment groups of patients with varying lengths of time for symptoms to disappear and observe how medication adherence rates differ among these treatment groups. It would be quite difficult to systematically change the length of time symptoms take to disappear in an RCT setting, but a modelling approach through lab experiment would allow me to test this relationship quite easily.

5.2 Example of modelling in behavioural science literature

In order to develop an experimental model for the non-adherent behaviour of patients taking antibiotics, I received inspiration from the work carried out by Judd B. Kessler and Alvin E. Roth (Kessler & Roth, 2012). They recently studied the organ donation policy and the decision to donate in a laboratory setting using an experimental game

modelling. I will briefly describe the problem that they addressed and the way they modelled the behaviour in an experimental game setting.

Organ donations from deceased donors are the major source of transplanted organs in the United States. However, most Americans are not registered organ donors. Kessler and Roth (2012) were interested in investigating how changes in the organ allocation policy would impact the registration of a person as a donor. In particular, their research considered deceased organ allocation policy that would give priority for receiving organs to people who themselves have registered to be an organ donor. They argue that such a policy would provide an incentive for people to register themselves as an organ donor.

Kessler and Roth (2012) used an experimental game modelling approach to study the effectiveness of the priority rule in increasing the registration of organ donors. They developed an abstract experimental game that did not involve actual organ donation decisions and neither did it use any organ donation terminology during the experiment. However, they imposed real (monetary) costs. Below is how the experiment was designed:

Participants of the experiment started playing a game where each round started with them having one “A unit” (which was researchers’ simulation of a brain) and two “B units” (which was researchers’ simulation of kidneys). In order to represent the flow of utility from being alive and healthy, every participant received $1 in each period in which they had both an active A unit and at least one active B unit. In every period, there was a 10% probability that participant’s A unit would fail (which would represent brain death) and 20% chance of failing of their B units.

Each round began with the participants having $2 and consisted of a number of periods that can allow them to earn more money (by keeping their A units and at least one B unit alive). The participants would lose $1 every time their A unit failed and the whole round would end for them, that is, there would no further periods in that round. If a participant's B unit failed, then they had up to 5 periods to receive a B unit from someone else (simulating the period of dialysis that patients go through while waiting for a kidney donation). If the participant fails to receive a donation of B unit from someone else during these 5 periods, then they would lose $1 and the round would end for them (representing onset of death). The B units of any player would only be donated to someone if that player registered at the start of the round to be a donor. The participants made donation decision 31 times in total and were paid based on their earnings in 4 randomly selected rounds.

In the control condition, participants were informed that the B units (kidneys) would be provided to those in need in the order that they were waiting for the B units. This control condition was the researcher's modelling of the current organ donation policy where the patients waiting in line the longest for a kidney transplant would be served first. The priority rule condition which the researchers were interested in investigating informed the participants at the start that those who agreed to be donors would be given priority should they need a B unit during that round.

Kessler and Roth (2012) found in the results of the experiment that the priority rule condition had a significant positive impact on organ donation registrations and they make a strong case in their paper to introduce the priority rule in the organ donation policy present in the United States.

The design of the experiment developed by Kessler and Roth (2012) inspired me to develop a similar experimental game that would allow me to simulate patient's pill-taking behaviour. It is important to accept here that one cannot model all features of the environment, behaviour and emotions of the patients in an abstract lab experiment but modelling does bring about its advantages as well (which have been discussed in Section 5.1). Moreover, the argument made in this thesis is not to replace RCTs with lab experiments but to introduce a modelling stage (through the use of lab experiments) prior to running an RCT when developing behaviour change interventions.

5.3 Non-Adherence Modelling Experiment

5.3.1 Objective

Before moving on to the design of the non-adherence modelling experiment and its results, it is worth recapping the motivation behind this dissertation and what has been established so far.

- We know that non-adherence to antibiotic medication is quite common and has serious consequences not only for the patients but also for the wider society (this was discussed in detail in Chapter 1).
- The most recent systematic reviews on medication adherence have identified that increasing the effectiveness of interventions aimed to improve adherence can have a greater impact than any improvement in specific medical treatment.
- The interventions to improve medication adherence are often divided into five categories: 1. Reinforcement: make treatment environments more appealing, 2. Education: communication information about best practice, 3. Provider support: direct educational or behavioural strategies at healthcare staff, 4. Affective:

change emotional or social influences through counselling or social support and 5. Behavioural: improve a patient's capacity to deal with taking medication. My focus in this thesis is on the last category, 'Behavioural'.

- Systematic reviews have found that the interventions to improve medication adherence have generally been effective but very few interventions were systematically developed, using appropriate theoretical models. Furthermore, most of the interventions were neither modelled nor piloted to really understand the underlying mechanisms that drive the non-adherence behaviour
- The Medical Research Council in the UK proposes that the development of any complex behaviour change intervention should follow the same cycle as drug development - a theory behind the design of the behavioural intervention, followed by modelling of the problem or behaviour, then an exploratory trial and finally a RCT and implementation of the intervention. My focus in this thesis was on the Theory and Modelling stages of the cycle.
- The 'Theory' stage of the MRC framework comprised of administering the Theoretical Domains Framework (TDF) to a national sample of the Pakistani population and we identified the key behavioural domains that exist as barriers towards patient's adherence to antibiotic medication (this was discussed in detail in Chapter 3).

Following on from the 'Theory' stage , we now enter the 'Modelling' stage. The objective in this stage is to develop a model that can capture the key elements of the real-world setting and also simulate the non-adherence behaviour of the patients taking antibiotic medication. Once a good model has been developed, it then serves as a platform to test

multiple interventions informed by the learning from the 'Theory' stage and subsequently taking the most successful interventions to the 'RCT' stage. In Section 5.2, we saw one example of how such a modelling exercise can be carried out using an experimental game which inspired the modelling methodology for my research.

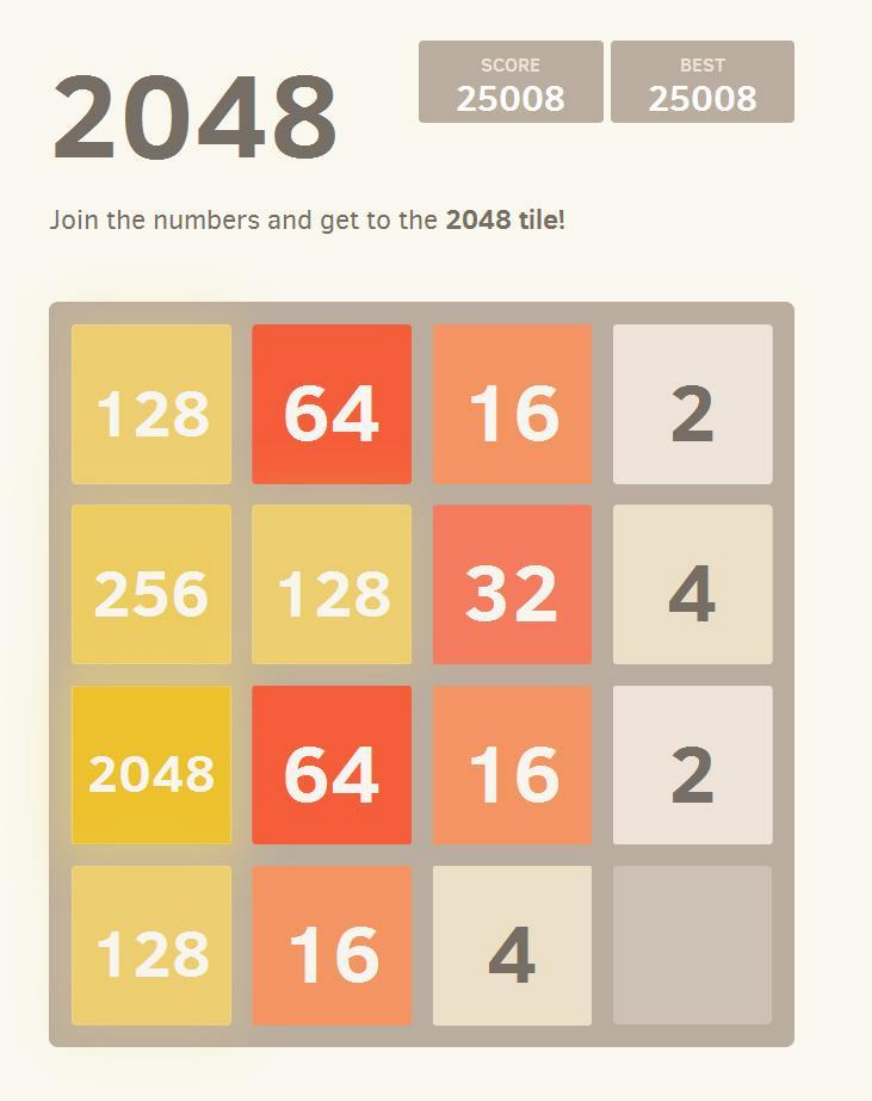
For the 'Modelling' stage, I have developed an experimental game using a popular and addictive video game called '2048'. The objectives of the experiment are twofold: Firstly: to model the non-adherence behaviour observed in the real-world setting (this would be the 'Control' group). Secondly: to test out a few interventions informed by the learning from the 'Theory' stage and judge the usefulness of the modelling approach.

5.3.2 Experiment Design

The lab experiment involved using a popular and addictive video game called '2048'. I will first explain briefly the mechanics of the original 2048 game and then move on to explaining in detail the design of the modified 2048 game which served as the control condition for the experiment.

5.3.2.1 Explaining the mechanics of Original 2048 game:

2048 is an open-source game. The game's objective is to move numbered tiles in such a way that the total adds up to 2048.



Screenshot of Original 2048 game

2048 game has a 4X4 grid, with numbered tiles that can be moved in four directions (up, down, right and left) by using the four arrow keys on the keyboard. Upon every turn, a new tile appears on one of the empty spots on the board with a value of either 2 or 4. Tiles move as far as possible in the direction of the arrow key that has been pressed until they are stopped by another tile or the edge of the board. If two tiles of the same number collide, then they merge together to form a single tile with the number being the

sum of the numbers on the preceding two tiles. So for example, to reach the final score of 2048, two tiles both carrying the number 1024 has to be merged; and in order to get a tile numbered 1024, two tiles both carrying the number 512 have to be merged and so on. When the player has no moves left, that is, there are no empty spaces left on the board and there are no adjacent tiles with the same number, the game ends. As soon as the game ends, an option appears on the screen for the participant to restart the game.

A scoreboard keeps track of the participant's score. The participant's score starts with a score of zero and it increments whenever two tiles with same numbers are merged.

The 2048 game was chosen for my experimental game modelling due to the following reasons:

1. It is an open source game, hence allowing me to modify the game to suit the needs of the experiment
2. The game is quite intuitive and it only takes a few minutes for a new player to learn how to play
3. The game is highly engaging, in fact during the course of the actual experiments several participants enquired and requested if they can take part in the experiment again as they really enjoyed themselves.

5.3.2.2 Explaining the mechanics of Modified 2048 game:

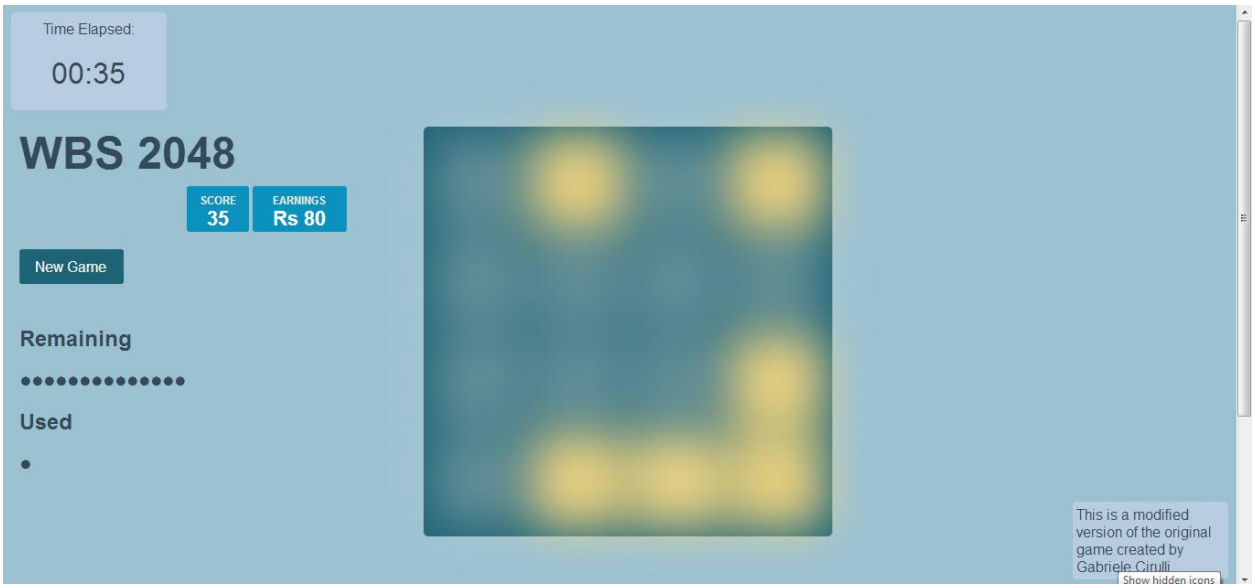
The original 2048 game was modified to create an abstract model for the medication adherence behaviour observed in real life. The game is the analogue of "everyday life". Participants were rewarded on how well they scored in the game. The sections below will

explain the design and mechanics of the Control condition and the 4 Treatment conditions.

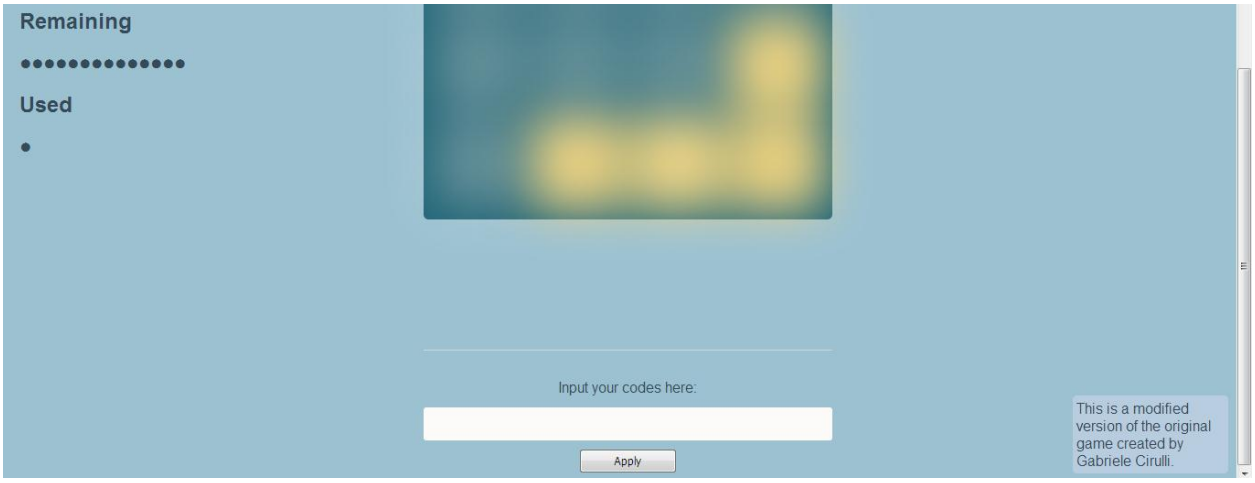
5.3.2.2.1 Control Condition

Concept

When participants start the game, the screen is blurred making it very difficult for them to play the game. This blurriness simulated the onset of illness. To simulate the use of medication, they were given a code which they entered every minute to clear the screen. The screen became clearer each time the code was entered. However, halfway through, the screen became clear while the participants were still expected to enter the code. If the code was not entered they could "relapse" and the screen became blurry again.



Screenshot of the experiment game right after participants start

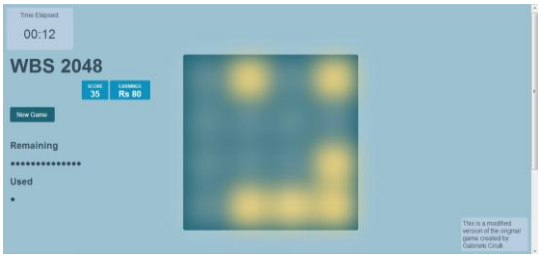


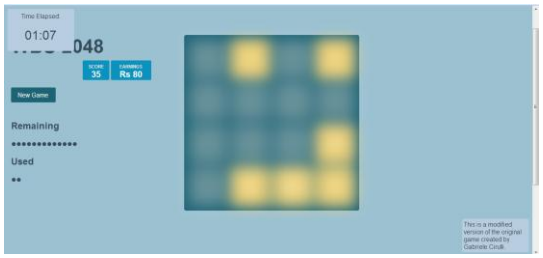
Participants had to scroll down to enter the code to clear the screen

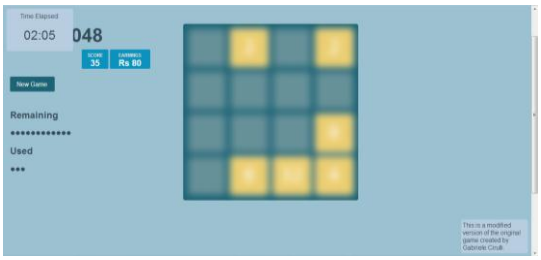
Specifics

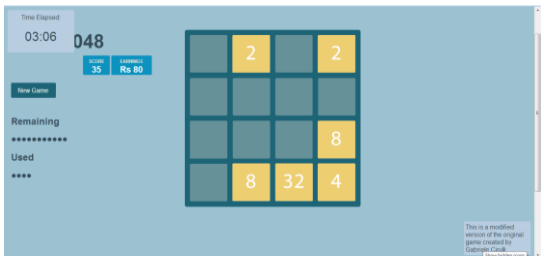
Blurriness

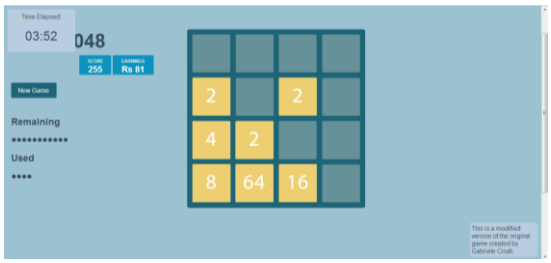
When participants start the game, the blurriness was set at 100% and each time they entered the correct code blurriness reduced by 25%. If they fail to enter the code, there was a 2% chance of "relapse", where the screen became blurry by 25%. The probability of "relapse" doubled each time the code was not entered. This mechanism of "relapse" activates in the experiment after the screen becomes clear for the first time. If a "relapse" had occurred, the participants were able to clear the screen again by subsequently entering a correct and on time code.











So on . . .

As participants keep entering the code every minute the screen became clearer

Duration

The total duration of the game was 14 minutes and 30 seconds, and the participants were instructed to enter the code every minute, therefore having had to enter the code 14 times in total. The 14 code entries simulated a typical seven day antibiotic medication course where patients are prescribed to take the pill twice a day with roughly twelve hour interval.

Text Box to enter code

At the bottom of the web page, a text box was placed where participants were asked to enter the code. The text box was placed such that in the default web page frame participants were not able to view the text box. Participants had to scroll down each time to enter the code, and once the code was entered the web page frame would come back to the game. The reason behind placing the text box out of view of the participants was to make sure that the text box itself did not serve as a cue or reminder to enter the code. In real life setting as well, patients do not always have the pill pack in sight.

Participants had to scroll down to enter the code to clear the screen

Time limit for code entries

A code was only accepted if it was correct and entered within 15 seconds at the start of every minute. For example, for the first time if participants entered the correct code between 1 minute and 1 minute 15 seconds, then it would have reduced the blurriness.

Similarly, the next time they were required to enter the code was any time between 2 minute past to 2 minute and 15 seconds past and so on.

Scoring

The scoring in the game was cumulative. It was based on the numbers on the tiles that merged together. So the higher the number on the two tiles that merge together the higher was the increment in the scores.

Code Entries

The participants were given the code on a paper strip and the code was *sd73hp8*. The alphanumeric nature of the code made it slightly difficult for participants to type every time and the slightly longer length of the code meant that it took a little longer for them to type the code in the text box. The difficulty produced by the nature of the code and the fact that participants had to scroll down every time to enter the code provided an analogue to the cost of taking a pill such as bad taste of a pill and side effects etc. Furthermore, participants could not copy and paste the code into the text box.

When participants entered the code, a message would pop out the content of which depended on the different scenarios:

- If the code was entered correctly and within the time limit, then the message said "Correct Code (on time)"
- If the code was entered correctly but was late, then the message said "Correct Code (wrong time)"
- If an incorrect code was entered, then the message said "Incorrect Code"
- If all codes have been consumed, then the message said "No Codes Remaining"

- If the code was entered correctly twice or more within the time limit, then the message said “Correct Code (already used)”

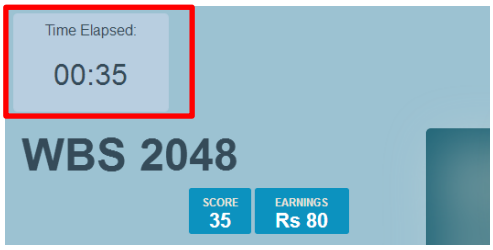
Pill counter

As an analogue to the pill pack, a pill counter was displayed on the left of the screen showing how many codes have been entered and how many were remaining. Participants received a total of 14 attempts to enter the code correctly, one for every minute. If participants used up all the 14 attempts before the end of the game then their codes were ineffective even if they were entered correctly and on time subsequently.

Pill counter was displayed on the left hand side of the screen

Timer

On the top left corner of the screen a timer was displayed which showed the time elapsed since the start of the game. The timer was there to assist the participants in keeping track of time so that they could enter the codes on time.



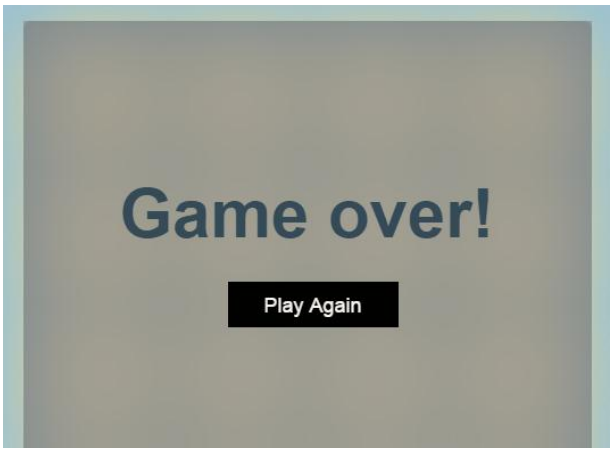
Timer was displayed on the top left hand side of the screen

Earnings

The show-up fee for the participants was Rupees Rs.80 (£0.50) and it was already included in the earnings; participants started the game with a score of 0 and earnings of Rs. 80. Once participants started the game, their earnings were proportional to their score.

Game Over

Participants were allowed to play the game as many times as possible in the duration of the experiment (which was 14 min 30 sec). Once a player had no moves left on the board, a message box popped up on the screen giving the participant an option to restart the game.



If the game ended during the experiment participants could start again

5.3.2.2.2 Treatment Condition 1: Incentive

The Theoretical Domains Framework (TDF) scorecard which was generated in Chapter 3 revealed "Reinforcement" as the lowest scoring domain. As was discussed in Section 3.5, the domain "Reinforcement" scored low in all three MMAS adherence categories. Essentially, once the symptoms went away and patients felt "all ok" there was not a lot of incentive for them to carry on taking their pills. This experience of symptoms going away earlier than the elimination of the disease is a very important and consistent phenomenon faced by patients with bacterial infections. Since this phenomenon is an inherent feature of the disease, patients do not have any control over it and hence we see low scores on "Reinforcement" among all three MMAS adherence categories rather than this domain affecting each of the three MMAS adherence categories differently.

The use of incentives to increase medication adherence has been studied in quite detail in the past. Ideally, incentives should provide frequent, small (but tangible) rewards.

Small rewards should be segregated from larger ones and there should be positive rather than negative incentives such as the use of lotteries rather than fines (Volpp et al., 2009). The use of such rewards may have the effect of "stamping" habit associations into the patient's memory. However, it is interesting to note Klein's (2009) position on the practice of rewarding patient behaviour with money. Klein (2009) maintains that rewarding behaviour with money may have the undesirable effect of devaluing the intrinsic benefits of adherence. Klein (2009) asserts that this may instead result in the creation of an even higher barrier to long term adherence. This leads to a suggestion of non-monetary incentive that keeps the same characteristics of frequent, small, tangible and immediate rewards. However, the views on whether incentives should be monetary or non-monetary are quite divided in the literature. The most recent systematic review on the use of incentives to increase medication adherence has found that incentive-based interventions can be quite effective in increasing adherence rates (DeFulioa & Silvermana, 2012). The review found that incentives that were small and frequent were more effective in increasing the adherence rates.

Following on from the results of the TDF National Survey, it seems appropriate to test whether providing incentives to patients to take their pills would improve the adherence rate or not. For the "Incentive" treatment condition, the design and mechanics of the experiment were exactly the same as the Control experiment except that participants were given an incentive of Rs. 5 (£0.02) every time they entered the correct code on time. This was extra bonus on top of their usual earnings in the game and the increment would show up in the earnings box on the top left corner of the screen. Also, when

participants entered the code correctly and on time, a flash message would appear on the screen informing them that they earned a Rs. 5 bonus.

The instruction video that participants watched before they start playing the "Incentive" version of the game explicitly mentioned the Rs. 5 bonus that they would earn upon entering the code correctly on time and the video shows one such instance where the code was entered correctly on time and the earnings increased by Rs. 5 (the instruction video is explained in detail later in Section 5.9)

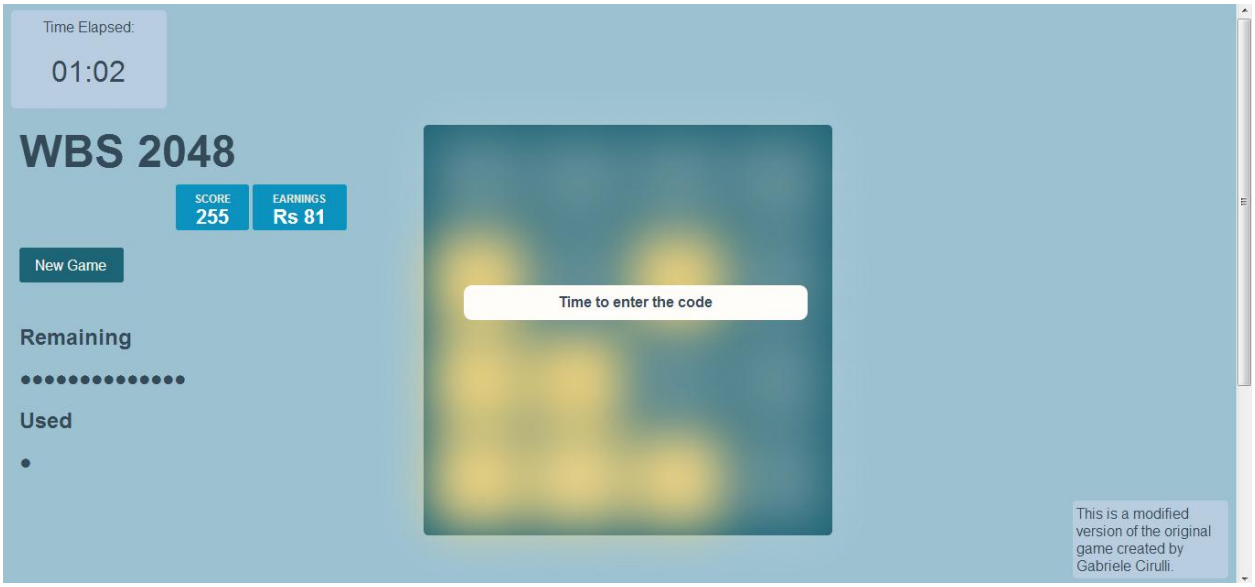
5.3.2.2.3 Treatment Condition 2: Reminder

The analysis carried out in Chapter 3 revealed that "Memory, Attention and Decision Processes" had a significant relationship with people's adherence rate to antibiotic medication. The MMAS questions further showed that 60% of the people said that they often forget to take their pills. It is quite natural for people to forget about taking their medication. This can especially be the case in situations where a person does not experience any symptoms of the disease. As the symptoms go away and the person is feeling better, he/she often gets distracted by their work, family and everyday life and simply forgets to take their medication.

The finding here seems to suggest that even though people want to take their medication, they often forget to do so. These results hint towards including some form of reminder mechanism in the development of any behaviour change intervention that addresses the issue of non-adherence to antibiotic medication. It therefore seems appropriate to test whether giving patients reminders to take their pills would improve adherence rates or not.

The most recent systematic review on the use of reminders to improve medication adherence found that overall reminders were successful in increasing the adherence rates of the patients (Veryloet et al., 2012). However, the review found that reminders were effective in increasing adherence rates in the short run only and it is still not clear how successful they can be in the long term. An antibiotic medication course is generally quite short (seven days) so the long-term effectiveness issue can be ignored in this instance.

For the "Reminder" treatment condition, the design and mechanics of the experiment were exactly the same as the Control experiment except that a message box would pop up on the screen when it was time to enter the code. The message box informed the participant that it was time to enter the code. This message box would appear in the middle of the board and stayed for a few seconds before disappearing.



A reminder message would appear on the screen when it was time to enter the code (this was only for the Reminder Treatment Condition)

The instruction video that participants would watch before they start playing the "Reminder" version of the game explicitly mentions that a reminder message would show up when it would be time to enter the code. The video also showed one such instance where it was time to enter the code and the message box pops up on the screen.

5.3.2.2.4 Treatment Condition 3: Commitment Device

At the time I was setting up my lab experiments, the Department of Health (DoH) was on course to run an RCT in collaboration with Boots UK on using a commitment device to improve medication adherence. They argued (as has been found in our research as well) that many patients want to take their medication but often fail to do so as they experience an 'intention-action' gap. The DoH decided to use a commitment device to minimize this 'intention-action' gap. Boots UK among many other pharmacies offers an NHS service called 'New Medicines Service'. The New Medicines Service (NMS) is a free service offered to first time patients who are prescribed a medicine to treat a long-term condition. It involves local pharmacist giving advice to patients about their new medicine. The pharmacist supports the patient over several weeks to use the medicine safely and to best effect; for example in handling or mitigating side effects. In particular there are three stages where a conversation takes place between the pharmacist and the patient: when the patient starts their medication; a follow-up phone call in two weeks' time; and another follow-up phone call two weeks after that. The DoH decided to use the first stage of conversation (when the patient starts their medication) to introduce the commitment device intervention and the other two stages of the conversation (two week and four week follow-up calls) to administer MMAS questions which served as their primary outcome variable. The main intervention for the treatment group involved

asking patients to sign a sticker stating that they commit to taking their medication as prescribed and then pasting that sticker on their medication package. There were two other treatment conditions which were variants of the main commitment device condition. DoH ran this study in 272 Boots pharmacies in London between July and December 2015 with a sample of 11,292 people.

Since one of the arguments that I am making in my dissertation is the need to include a modelling stage before running an RCT rather than jumping straight into an RCT, I decided to include as one of my treatment conditions in the lab experiment the same commitment device that DoH and Boots UK were using in their RCT. Although this will not be a fool-proof validation of my experimental model it would at least allow us to compare the results I get in my lab experiments on the improvements in adherence rates versus what has been achieved in the RCT run by DoH.

For the "Commitment Device" treatment condition, the design and mechanics of the experiment were exactly the same as the Control experiment except that at the start of the experiment participants were asked to sign a sticker stating that they commit to entering the code as prescribed. The sticker was then pasted on the laptop that participants were using to play the experimental game. Participants watched the same instruction video as the 'Control' condition.

The commitment sticker was pasted on the laptop that the participants were using to play the experimental game (this was only for the Commitment Device Treatment Condition)

5.3.2.2.5 Treatment Condition 4: Elongated duration for Symptoms

In the development of a behaviour change intervention, a researcher might be interested in investigating the effects of various factors or interventions that are not quite straightforward to test in an RCT. Modelling allows for manipulations that cannot be reliably or systematically manipulated in the real setting. In order to showcase this strength of the modelling approach, I decided to investigate the relationship between the length of time that symptoms exist and the adherence rates of the patients. Systematically changing the length of time symptoms take to disappear is quite impossible to manipulate in a real-world setting but understanding the relationship between symptoms and medication adherence rates is very important. We have already

observed in Section 3.4 that more than one-third of the people admit that they stop taking their antibiotic medication once they feel better and their symptoms go away.

I believe that symptoms provide a special kind of feedback to the patient that is endogenous in nature. As patients start their antibiotic medication course, their symptoms start to disappear. This gradual improvement in health (experienced by disappearance of symptoms) serves as an implicit feedback to the patient that the medication is working and it is helping them get better. Once the symptoms are gone, the patient feels better and does not experience or feel any more positive effects of taking the antibiotic pills. There is no more "endogenous" feedback on the behaviour of taking the antibiotic medication and hence we observe a reduction in adherence rates.

It is to be noted that normally feedback means telling people how they are doing, but here it is useful to distinguish between the feedback that comes from an action directly (we remove our hand from the hot stove and the pain stops), and feedback provided by a helpful outsider (when we get near a hot stove a red warning light goes on). All the conditions contain some feedback in that the number of pills used and remaining is provided onscreen. The symptom is a kind of feedback, but it is a special kind.

In an ideal setting, I would have liked to have a few treatment conditions with varying lengths of time for symptoms to disappear. However, keeping the time and cost constraints in mind I decided to include one treatment condition where it would take twice as long for the symptoms to disappear compared to the control condition. For this "Elongated Duration for Symptoms" treatment condition, the rest of the design and mechanics of the experiment were exactly the same as the control experiment. Participants watched the same instruction video as the 'Control' condition.

5.4 Setting up of lab in Pakistan

In order to run my experiments I needed a lab in Pakistan. Given that I used Gallup Pakistan for the two national surveys that have been described in Chapters 3 and 4; I developed a good working relationship with them. Gallup Pakistan has been quite keen on expanding their range of services to include behavioural science expertise and as such, their senior management was very willing to provide space and managerial assistance to set up a lab. With Gallup Pakistan, I set up the first behavioural science lab in Pakistan.

I set up two labs, one in Islamabad and the other in Karachi both using the vacant office space in Gallup's main city offices. Both the labs were used for testing and piloting of the experiments and also for the actual experiment itself.

The lab that was set up in Islamabad

It is important to address the question of why the research in this thesis was carried out in Pakistan. Below I explain a few reasons:

- There is a critique of running lab experiments with WEIRD participants; participants belonging to 'Western, Educated, Industrialized, Rich and Democratic' societies (Henrich et al., 2010). WEIRD participants only account for 12% of the world population and therefore it is difficult to generalize the results of the findings to a population that differs quite substantially from it. I wanted to move away from WEIRD participants and decided to use Pakistani public as participants for my lab experiment. In fact I managed to go an extra mile and with the help of Gallup Pakistan managed to recruit a representative sample of the Pakistani population that are computer literate for my lab experiment. This meant that the behaviours observed in my lab experiment and the results found can quite well represent the Pakistani population as a whole. Behavioural science as a field is yet to enter the academic circles in Pakistan let alone its use in the applied setting. So I saw this as an exciting opportunity to also introduce behavioural science research in Pakistan
- Non-adherence to antibiotic medication is worse in developing countries (WHO, 2003) and subsequently the threat of AMR is greater in these countries as well. Pakistan is the 6th largest country in the world based on population and the results of MMAS in Chapter 3 shows the severity of non-adherence problem in Pakistan. With large proportions of the population falling into the "High" and "Medium" adherence categories, there was a strong case for my research to create a meaningful impact. There also does not exist much academic literature on the extent of adherence to antibiotic medication among the Pakistani population and I saw this as an opportunity to contribute my work.

- The difference in economic conditions between the UK and Pakistan meant that I could recruit a much bigger and richer (in terms of socio-economic demographics) sample for my lab experiment in Pakistan than in the UK. For the same financial resources that would allow me to recruit University of Warwick students to participate in my experiment in the UK, I was able to recruit a much larger sample of a representative Pakistani population. Since I was able to recruit a representative sample for the general public for my lab experiment, a stronger case can be made for the findings from this research.

5.5 Participant recruitment

The recruitment of participants for the lab experiments was carried out through Gallup Pakistan. They already had a system in place for recruiting people for focus groups and I used the same system to recruit people for the experiments.

Since participants of the lab experiments had to play a computer game, the participants were screened on the basis of whether they were computer literate or not. A significant proportion of the Pakistani population does not know how to use a computer which restricted me to recruiting a representative sample of the computer literate Pakistani population rather than a representative sample of the whole Pakistani population.

In order to get the representative proportions of the computer literate group, I used Gallup Pakistan's data on the number of people who use internet in the country and how that group was split across gender and education levels. I was not able to find national proportions on computer literacy and hence used 'being able to browse on the internet' as a proxy for computer literacy. Below are the representative proportions in which the

participants were recruited for my lab experiments (each of the control and treatment groups had the same representative proportions).

Education	**Proportion**
Middle to HSSE (Current)	25%
Middle to HSSE (Past)	30%
Undergraduate/Postgraduate (Current)	25%
Undergraduate/Postgraduate (Past)	20%

Gender	**Proportion**
Males	60%
Females	40%

'Middle' corresponds to O' level education level in the UK and HSSE corresponds to A' level education in the UK.

'Middle to HSSE' and 'Undergraduate/Postgraduate' were split into two groups. The first comprised of participants who were currently studying in either of those two levels of study. The second comprised of those participants who had already completed either or both levels of study and who had not gone beyond that education level.

Gallup Pakistan provided transport facilities to any participants who requested for it. This was especially the case with female participants as it was quite difficult to recruit them otherwise. Due to cultural sensitivities, gender barriers can be faced by females in

various scenarios. The whole recruitment exercise required us to be culturally sensitive and also to respect the work commitment of the participants. In some instances the timing of the running the experiment was adjusted to accommodate participants after office hours.

5.6 Payment mechanism

The participants of the lab experiments were paid a show up fee of Rs. 80 (approximately 50p) and their further earnings were based on how well they performed in the experiment. The earnings of the participants were proportional to their score in the game. The maximum money that participants could earn was Rs. 500 (approximately £3). The game itself was 14 minutes and 30 seconds in its entirety. However, inclusion of the initial practice rounds, instruction video and payment process brought the whole exercise to 30 minutes on average.

At the end of the experiment, the final score and earning of the participant showed up on the screen along with their participant number which served as an ID. The participant ID and the earning were recorded on the payment sheet and participants were paid the money in cash accordingly. Each participant was requested to sign confirming the receipt of the payment.

5.7 Piloting the 2048 experiment

The final version of the control and treatment experiments that have been described in Section 5.3 came about after a series of testing and piloting with participants in Pakistan. In this section I briefly describe the observations that were made during the pilot tests, the improvements that were made in the design of the experiments and the preceding reasons.

5.7.1 Duration of the game

The initial design of the experiment had the duration of the game set at 28 minutes during which participants had to enter the code every 2 minutes. During the pilot experiments I observed that participants became quite bored after about 15-20 minutes. The body language of the participants and their game play both led to my judgment. This observation was further substantiated by the feedback that I got from participants at the end of the experiment. Since a typical antibiotic medication course requires the patient to take the medication twice a day for 7 days; 14 pills, I wanted to simulate this by having the participants enter the code 14 times in total. After the feedback from the pilot, I decided to reduce the total duration of the game to 14 minutes and 30 seconds instructing the participants to enter the code every minute rather than every two minutes.

5.7.2 Season when experiments were carried out

I carried out some of the pilot experiments in December 2015 which is during winter in Pakistan. The lab that was set up at Gallup's office was in a very quiet location. The experiment involved participants using the up-down-right-left arrow keys on the keyboard to play the game and the mouse attached to computer was only used to scroll down so that participants could enter the code. Since the environment was very quiet, the sound of pressing the keys on the keyboard and clicking of the computer mouse was enhanced. I was able to judge when any participant entered the code by the sound of a sudden drop of the key followed by mouse clicks. I observed during my pilot tests that these auditory changes at the time of entering the code were setting prompts for other participants to enter the code as well. During the conversation after the end of the

experiment, I checked with a few participants whether the clicking sound of the mouse by the neighbouring participant gave them a cue to enter the code, however according to them that was not the case. However, just to avoid any contamination of the results the actual experiments took place during a warmer season which meant that the noise of the fan and air-conditioning effectively cancelled out the sounds from the keyboard and the mouse.

5.7.3 Window of time when code could be entered

In the initial design of the experiment, the window of time that participants had to enter the code started from 10 seconds to the minute until 10 seconds after the minute. For example, for the first code entry participants could enter the code any time between 0 minutes 50 seconds until 1 minute 10 seconds and the code would work by reducing the blurriness of the screen. Some participants in the pilot tests found this window of time very confusing even though the instruction sheet clearly explained when the start and end time would be for the participants to enter the code. Upon this feedback, I changed the starting time to be exactly on the minute and then participants had 15 seconds to enter the code for it to be effective. I tested this change with a few participants in a subsequent pilot test and the matter was resolved. Hence, in the final design of the experiment (explained in Section 5.3), the time to enter the code started at every minute and lasted for 15 seconds.

5.7.4 Analogue of consequence of non-adherence

One factor that took a bit of time to get right during the pilot tests was the analogue of the consequence of not taking the pills. In the real-world setting, the consequences of not taking the pill are issues such as relapse of the disease and increased resistance to the antibiotics but these costs are further in the future and not very salient. I needed an analogue for the consequence of non-adherence that would not be very immediate and salient. In the initial design of the experiment, the participants were told that the number of correct on-time code entries would be recorded at the end of the experiment. I would then put a corresponding number of white paper strips in a box and then add black paper strips so that the total number of strips in the box would come to 14. Participants would then choose a strip at random and if it turns out to be a white strip then he/she would be paid the full amount earned in the game, else he/she would be paid only the show-up fee. For example, if a participant entered the correct 10 times on-time i.e. he/she took the pill only 10 times out of 14, then I would put 10 white strips and 4 black strips in a box and let the participant blindly pick a strip and pay accordingly. The results of the pilot tests with this design revealed that almost all participants were adherent. I believe that the consequence of non-adherence was very salient using the box and strips. This was more so the case because I had to demonstrate to the participants before the start of the experiment how the box and strip method would work. Even though I had this box and strip method of payment written down in the instruction sheet that I would hand out to the participants before the start of the experiment but the participants were finding this confusing so I started demonstrating the box and strip process. I believe that this led to the consequence of non-adherence becoming very salient and hence not the best of analogues for my experimental game

modelling. Since the adherence rates that I was getting in my pilots of the control experiment were very high, they were not really comparable to the adherence rates observed in real world.

I then moved to the other extreme and carried out a few pilot tests with no consequence of non-adherence (all else remained the same). The results showed that there was much more non-adherence in these pilot test which was expected as there was no consequence of not entering the code. However, there was a serious criticism to this approach as there was no analogue of consequence and only the people in the incentive treatment group would have an incentive to take the medication and thereby enter the code.

The final design of the experiment (explained in Section 5.3) incorporated the consequence of non-adherence in the following way: When participants started the game, the blurriness was set at 100% and each time they entered the correct code the blurriness was reduced by 25%. If they failed to enter the code, there was a 2% chance of a "relapse" where the screen became blurry by 25%. The probability of a "relapse" doubled each time the code was not entered. This mechanism of "relapse" activated in the experiment after the screen became clear for the first time. If a "relapse" had occurred, the participants were able to clear the screen again by subsequently entering a correct code on time.

5.7.5 Game play

Since most of the people participating in my lab experiments were not familiar with the game 2048, I first showed them how the original game is played and gave them practice time. There is a very quick learning curve for 2048 and after about 10 minutes of play every participant was quite comfortable with the game. In my initial pilot tests, I showed

participants how to play the original 2048 game, gave them practice time, handed out the instruction sheet and then asked them to start playing the experimental game. However, since there was a considerable difference between the original 2048 game and the modified version (which included the blurriness aspect and code entry) many participants got confused and did not understand the code entering process. Upon this feedback, I included a demonstration of how to play in the actual experiment as part of the participant's orientation. So for each of the control or treatment conditions, I would show them on a multimedia how to play in that particular control or treatment condition and explained the features that were different from the original game such as timer, pill counter, blurriness and entering the code. In essence, I showed a demo of the instruction sheet that was provided to the participant. This short demo of how to play in the actual experiment improved the modelling of the real-world scenario. People are quite used to taking an antibiotic medication course and it is not a novel exercise. Most of the participants in my experiments were playing the original 2048 game for the first time and none of them had played the modified version of the game in my experiment; the experimental game that I was using in my experiment was completely new to them. As a result, introducing the practice session to play the actual 2048 game and giving a demo of what to expect and how to play the modified version in my experiments made a stronger case for an analogue to the real-world setting.

In order to ensure that exactly the same demo was given every time before the start of the experiment, I recorded a video of the game screen with my voice over. This video was used in all the actual experiments that were run.

5.7.6 Experiment instructions

The first screening criterion to recruit participants for my lab experiments was for them to be computer literate. For the initial pilot tests I prepared the instruction sheet in English assuming that if participants are computer literate then they would be able to read and understand English as well. I observed in the first few pilot tests that all participants were able to read the English instruction sheet but some of them did not really understand the instructions. I realized this from the way they played in the experimental game and also from having a focus group conversation with them after. In order to avoid any misunderstanding of the instruction sheet, I prepared an Urdu version of the instruction sheet as well and at the start of the pilot tests, offered participants the choice between Urdu and English instruction sheets. I realized that when I offered the choice between Urdu and English instruction sheets, all the participants opted for the English instruction sheet even though I knew that some of the participants might not be able to completely understand the instructions in English. This behaviour is likely to derive from the perception of English as a status symbol in Pakistani society. Oftentimes, knowledge of the English language is used as a measure of an elite and socially acceptable education. This is reflected by English being the official language of Pakistan (even though the national language is Urdu). I felt that some of the participants in my pilot tests chose the English instruction sheets (even though some of them didn't completely understand the English instructions) to signal to myself and the rest of the group that they are proficient in the language.

I wanted to make sure that all the people taking part in my experiment completely understood the instructions and the game play of my experiment while avoiding the

English/Urdu instruction sheet problem. I therefore decided to develop an instruction video in Urdu explaining all the content that was written in the instruction sheet. The video also provided me with the opportunity to include the demo of the actual experiment. Furthermore, in the real-world setting a verbal communication takes place between the GP and the patient at the time of antibiotic prescription (in Pakistan, the language used in Urdu). Therefore, using an instruction video made a stronger case for an analogue to the real-world setting.

5.7.7 Some validation of the modelling experiment

In one of the pilot tests the participants knew each other and I observed after the end of the experiment they were comparing their scores and also how many times they entered the code. One of the participants commented that he stopped entering the code because the screen was clear. I interviewed another participant after the experiment finished and she stated that she remembered that if she did not enter the code the screen would become blurry again (this demonstrated that she knew the consequence of non-adherence) but then she missed the code entry one time and nothing happened so she relaxed thereafter. One other common theme that emerged from interviewing the participants was that they simply forgot to enter the code because they were engaged in the game. These comments from the participants of the pilot testing mimicked quite closely the statements of patients that were discussed in Chapter 3. I acknowledge of course that these qualitative statements are not enough to justify the validity of the modelling experiment (in terms of its simulation of patient's behaviour) but it was a very positive sign to see that the experiment was generating the same behaviour and feeling as were noted among the patients.

One of the initial pilot tests where I used a multimedia projector to give a demo of how to play in the experimental game

5.8 Explaining the steps participants went through during the lab experiment

Gallup Pakistan recruited the participants based on the demographic profile that I shared with them. To many of the participants, Gallup provided a transport facility to make it easy for them to participate in the study.

5.8.1 Lab arrangement

The arrangement of the room is described below.

Each desk had:

- A laptop;
- Keyboard;
- Mouse;
- Internet connection;
- Google Chrome on the computer system and
- Headphones.

On every laptop an Incognito window was opened in Google Chrome. In this window, three tabs were opened:

- A tab with the original 2048 game: https://gabrielecirulli.github.io/2048/
- A tab with the instruction video
- A tab with the study game: http://leaders.wbs.ac.uk/umar/index.html?cond=X; where X was replaced with the condition number that the participant was playing. So if it was Condition 0 then X was replaced with 0 and so on…

There was a separating mechanism between each desk so that the participants were unable to see each other's screens.

5.8.2 Participant journey

Below was the journey that the participant went through during the whole experiment exercise:

- Once all the participants arrived at the Gallup office, they were directed to the lab and seated by the desks. I welcomed them all and asked them to switch off their mobile phones

- I distributed the participant information leaflet and asked them to read it carefully
- This was followed by distributing the consent forms to each participant and requesting that they sign it if they agreed to carry on with the experiment exercise (Appendix 1 shows the participant information leaflet and the consent form which was distributed).
- Participants were then asked to open the original 2048 game tab. I explained how the original game worked and walked around to each participant to make sure that they had the original game tab opened and understood how to play the game. Participants were given 10 minutes to practice playing the original 2048 game.
- While the participants practiced the game, I collected the consent forms and distributed the code slips
- At the end of the practice round, each participant was asked to close the original 2048 game tab and was directed to open the instruction video tab. The instruction video explained in detail how to begin playing the experimental game and also gave a demo of the experimental game (this demo varied depending on the control and treatment conditions that the participants were in)
- Once the participants had finished watching the instruction video, they were asked to begin the experimental game
- It took 14 minutes 30 seconds for the experimental game to finish, and at the end of the experiment I walked around to each participant, recorded the participant number and the amount of money earned

- The participants were then paid the amount that they earned in the experimental game and were asked to sign a receipt confirming that they were paid. This marked the end of the whole experiment exercise

5.9 Instruction video

I discussed in detail the formative research that was carried out to understand the communication that takes between the doctor and the patient at the time of prescribing antibiotic medication (details can be found in Chapter 4). The motivation behind that exercise was to ensure that I communicated exactly the same points in my experiment instructions that the doctor communicates to the patient.

The initial design of the experiment involved handing out written instruction sheets to the participants (this has been explained in Section 4.10) explaining the experimental game but after various pilot tests and feedback from the participants I decided to instead have an instruction video. Giving out instructions in a video format was in fact a better simulation of the real-world setting since the doctor also has verbal communication with the patient at the time of prescribing medication. Furthermore, an instruction video ensured that exactly the same content was delivered to each participant and took away any biases that I might have created whilst giving demo to the participants.

I recorded the instruction video using CamStudio which is a free, open source desktop recording software. Three instruction videos were made in total. The instruction video for the control group was also used for the “Commitment Device” treatment condition and the “Elongated duration for Symptoms” treatment condition. For the “Incentive” and “Reminder” treatment conditions, all the content of the video was exactly the same

as the instruction video for the control condition except that they included additional details showing an instance of how the incentive would work (for the "Incentive" video) and how the reminder message would appear on the screen (for the "Reminder" video). The actual videos can be viewed online here:

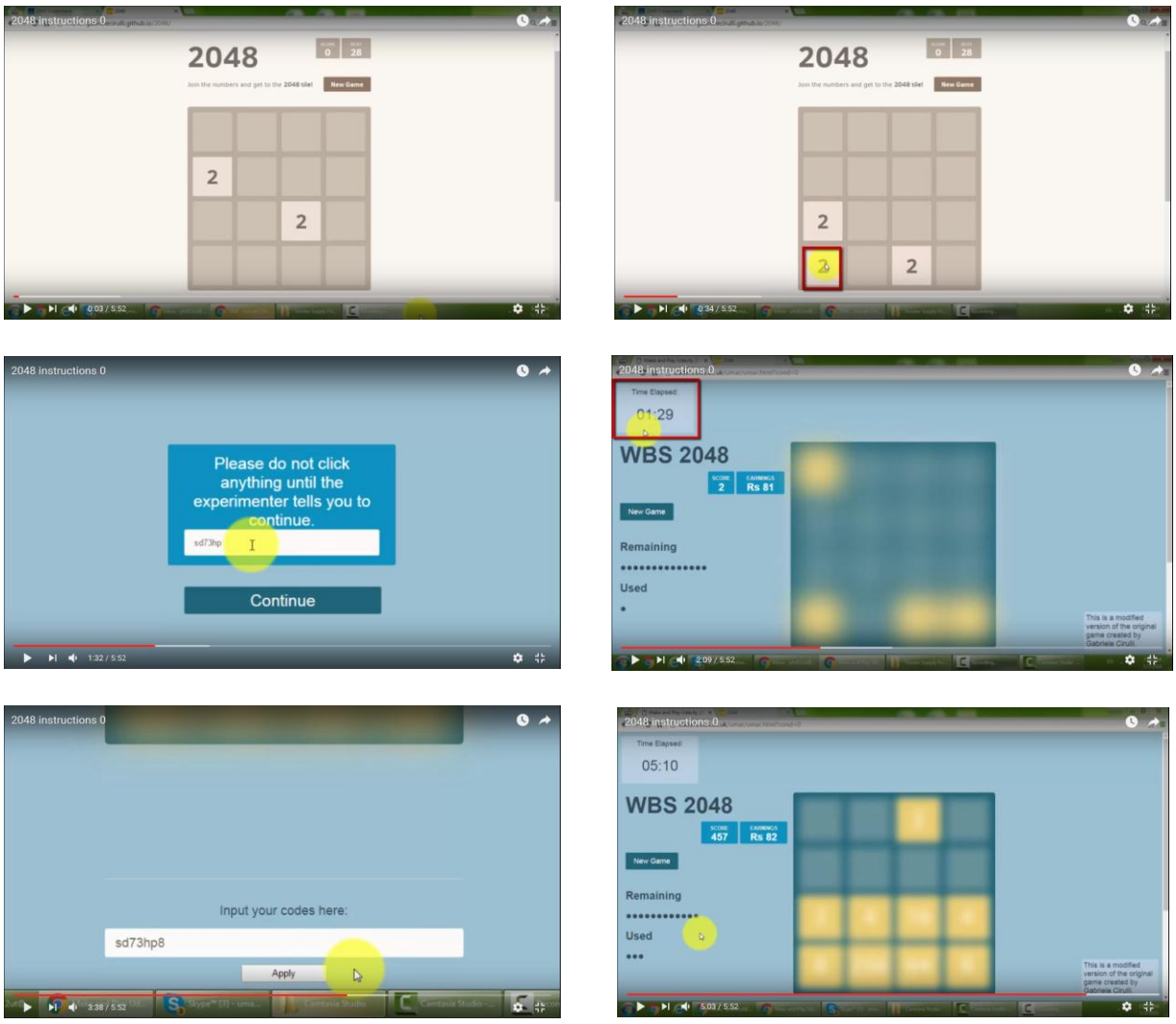
Control condition/"Commitment Device"/ "Elongated duration for Symptoms" - https://www.youtube.com/watch?v=_EzNBppFXoU&t=4s

"Incentive" treatment condition - https://www.youtube.com/watch?v=yFGFEedweTE&t=4s

"Reminder" treatment condition - https://www.youtube.com/watch?v=6dKyLSig5sk&t=7s

From the formative research that I carried out (explained in Chapter 4), I was able to conclude that the following key points are communicated to the patients by the doctor at the time of medication prescription:

- Which medicine to take
- How often to take the medication
- How long the medication should be taken
- The consequences of not completing the medication course
- That the medication course must be completed and not left half way through



A few screenshots of the instruction video that was used for the control condition

Below I describe the analogue for each of these points that were communicated to the participants of my lab experiments in the instruction video:

Formative research	Analogue in the instruction video
Which medicine to take	Participants were given a code slip which clearly stated the code that was to be entered to help clear the screen. The instruction video referred to the code slip.
How often to take the medication	The instruction video clearly mentioned that the code needed to be entered every minute and two such instances were shown in the video where the code was entered and the reduction in the blurriness of the screen was observed. The window of time during which the code needed to be entered was also explained very clearly in the instruction video.
How long the medication should be taken	The instruction video clearly stated that the code needed to be entered 14 times in total, and that the total duration of the game was 14 minutes and 30 seconds.
The consequences of not completing the medication course	It was communicated to the participants in the instruction video that if they did not enter the code on time then it was likely that their screen would become blurry again.
The medication course must be completed and not left half way	The participants were told in the instruction video that they must enter the code 14 times in total.

5.10 Results and discussion

The experimental results are from 509 participants who participated in my lab experiment. There were 104 participants in the control group; 106 participants in the "Incentive" treatment group; 97 participants in the "Reminder" treatment group; 102 participants in the "Commitment Device" treatment group and 100 participants in the "Elongated duration for Symptoms" treatment group.

There were 23 participants (4.5% of the sample) who played the game but did not make any code entries in the experiment. However these participants were found in all groups: 7 in the Control condition, 5 in the "Incentive" condition, 3 in the "Reminder" condition, 3 in the "Commitment device" condition and 5 in the "Elongated duration for symptoms" condition. It might be that these participants did not understand the instructions related to code entries or that they were not interested in the experiment itself. The data of these participants was subsequently removed for any analysis.

5.10.1 How adherence rates varied between conditions?

Planned comparisons (ANOVA) were carried out to determine significant changes in adherence rates between the control group and treatment groups. The adherence rate in the control group was 44%.

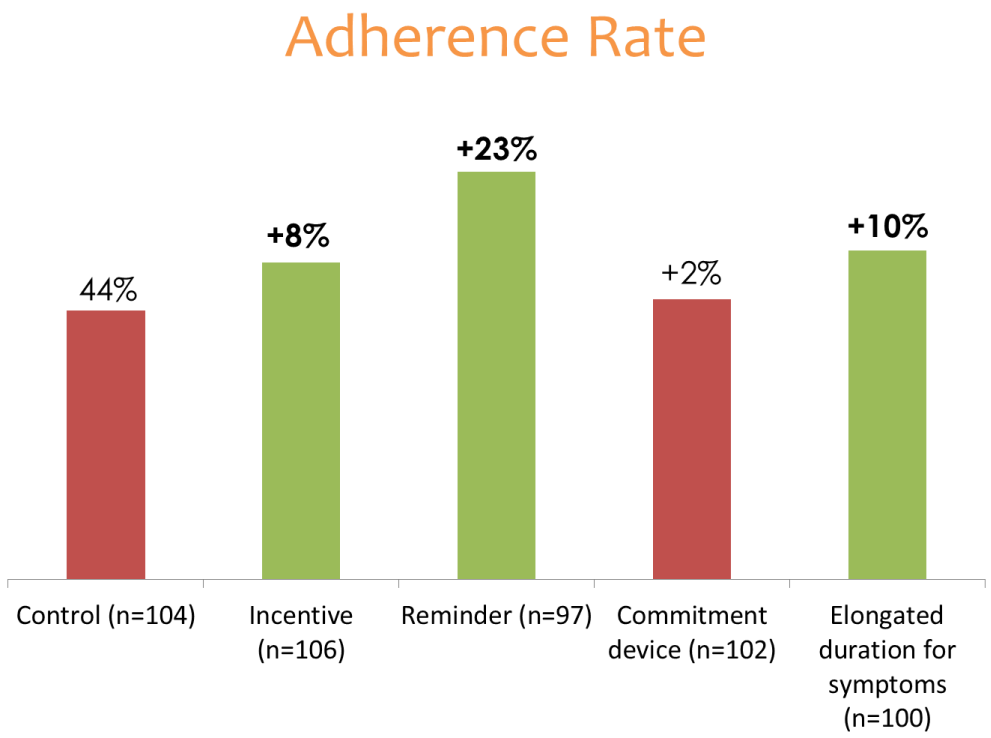
Reminders improved the adherence significantly by 23% ($p<0.0001$). The behavioural diagnosis that was carried in the 'Theory' stage (referring to the research mentioned in Chapter 3) did reveal that "Memory, Attention and Decision Processes" had a significant relationship with people's adherence rate to antibiotic medication. The MMAS questions further showed that 60% of the people said that they often forget to take their pills. The

finding here suggests that simply reminding people to take their antibiotic medication can improve medication adherence significantly. I discuss the implications of this result and how it fits with the general literature on the use of the reminders to improve medication adherence in the next chapter.

In the "Elongated duration for Symptoms" treatment group, the adherence rate improved significantly by 10% (p=0.017). This is a very interesting result, as the motivation behind including this treatment (doubling the time it takes for symptoms to go away) was to show how modelling allows for manipulations that cannot be reliably or systematically manipulated in the real setting. It was almost impossible to test systematically in the real-world setting how the adherence rate would change depending on the duration symptoms last. However, the results of the modelling experiment suggest that adherence rate increases if it takes longer for symptoms to disappear. This result and its implication are discussed more in the next chapter.

Incentives improved the adherence significantly by 8% (p=0.042). The Theoretical Domains Framework (TDF) scorecard that was generated in Chapter 3 revealed "Reinforcement" as the lowest scoring domain. In fact, the domain "Reinforcement" scored low in all three MMAS adherence categories (see Section 3.5). Essentially, once the symptoms go away and patients are feeling "all ok" there is not a lot of incentive for them to carry on taking their pills. It seems from the results of the modelling experiment that providing people with incentives to take their medication can improve adherence rates. I discuss the implications of this result and how it fits with the general literature on the use of the incentives to improve medication adherence in the next chapter.

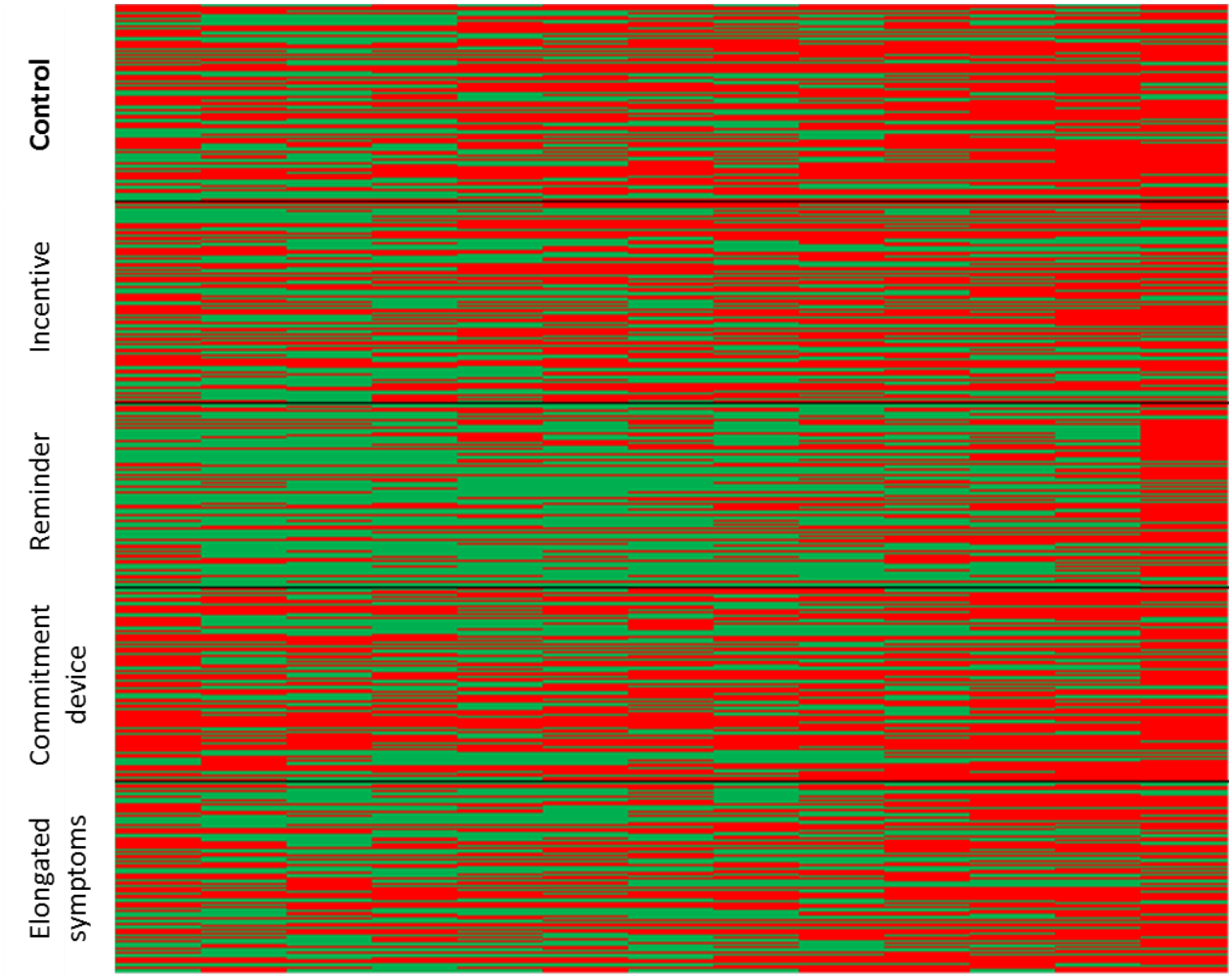
The commitment device did not bring about any change in the adherence rate compared to the control group. My main motivation behind including a commitment device as one of the treatment groups was to replicate the DoH and Boots UK RCT trial where they were asking people to sign a commitment sticker. I was interested in comparing the results of the RCT with my modelling experiment. At the time of writing this dissertation, the results of the DoH and Boots UK RCT had been released (the DoH team is in the processing of publishing the paper, but they have presented their results in multiple academic gatherings) and interestingly the commitment device did not bring about any change in the adherence rates in the RCT trial as well. I discuss this result more in the next chapter.



A significant increase in the adherence rate was found in the "Reminder", "Elongated duration for Symptoms" and "Incentive" treatment condition

5.10.2 Visual display of participant entries

The image below shows a visual representation of how each participant entered the code. A red colour indicates that the person did not take the pill while a green colour indicates that the person did take the pill. The black lines split the control and the treatment groups. It can be seen generally that there is more green in the initial phase of the experiment when the screen was blurry as compared to the latter stage, showing that adherence was higher at the start of the experiment when the screen was blurry (while symptoms are there) and decreased once the screen became clear (when symptoms are gone). I analyse this observation in more detail later. It can be seen visually that the reminder condition has a lot more green compared to the control and the same is true for the “Elongated duration for symptoms” condition. Even though the statistical tests confirmed which treatments worked and which didn’t, it is interesting to visually see the difference as well.



Data of all participants split by control and treatment groups. Red indicates that a pill was missed and green indicates that a pill was taken

5.10.3 Analysis of the code entries

With regards to the kind of code entries, 63% of the code entries were correct and on time across all conditions. 21% of the code entries were correct but they were entered at the wrong time. This seems like a fairly reasonable result as it is not too impossible to expect that some patients might take their pill at the wrong time. 7% of the code entries consisted of wrong codes which translate to a few patients taking the wrong pill. This

result can be justified as patients who are on complex medication regimens (such as tuberculosis) do sometimes take the wrong pill.

5.10.4 Effect of symptoms on adherence rates

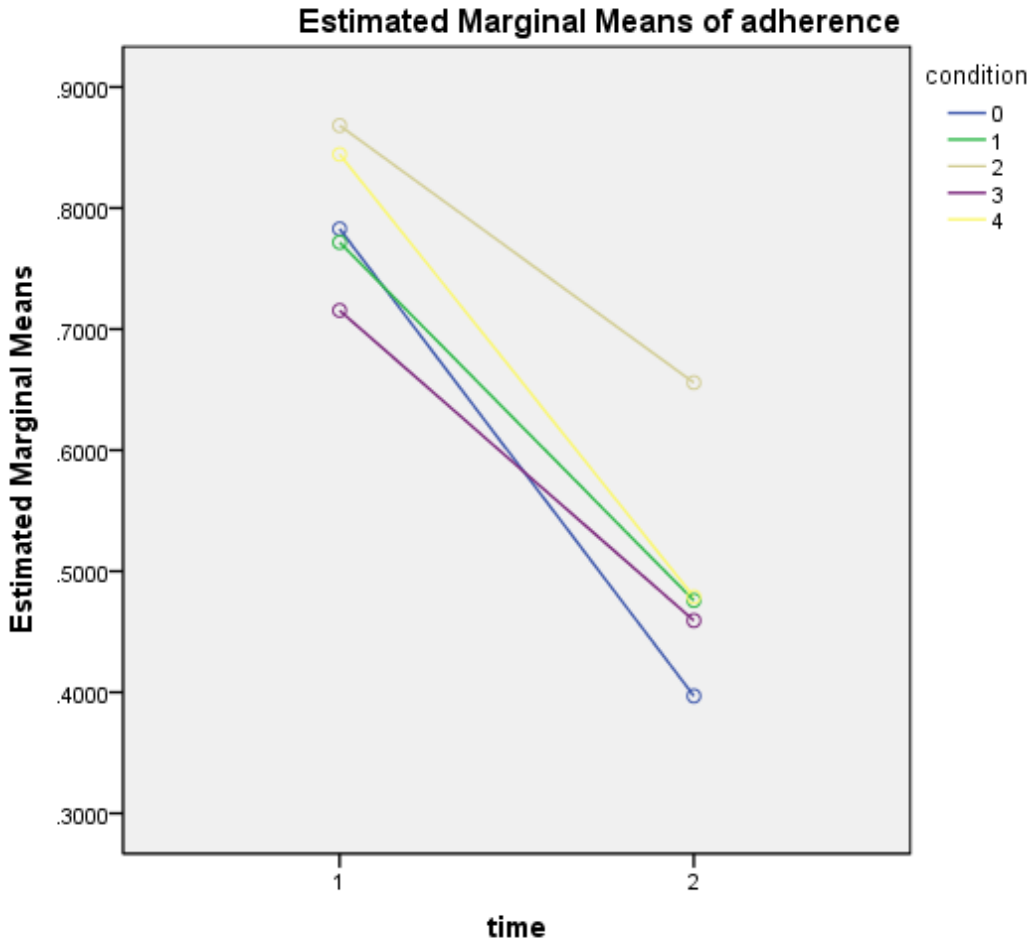
I have discussed on separate instances in the previous chapters how existence of symptoms plays an important role in the adherence rate of the patients. The main analysis of the experiment results showed that in the "Elongated duration for symptoms" condition where it took longer for symptoms to disappear (for the screen to become clear) participants were more adherent. The visual representation of the code entries of all participants (referring to the red/green image) also showed more green in the initial stages of the experiment (that is, when the screen was blurred). Therefore I carried out a detailed analysis of how the adherence rate changed once the screen of the participants was cleared (once the symptoms were gone).

The plot below shows how adherence rate varied between two time periods:

Time 1 = while the screen was blurry for the participants

Time 2 = once the screen became clear

The conditions were coded as: 0 for Control condition, 1 for "Incentive", 2 for "Reminder", 3 for "Commitment device" and 4 for "Elongated duration for symptoms".



Adherence rates while the screen was blurry (symptoms were present) and after the screen cleared (symptoms were gone)

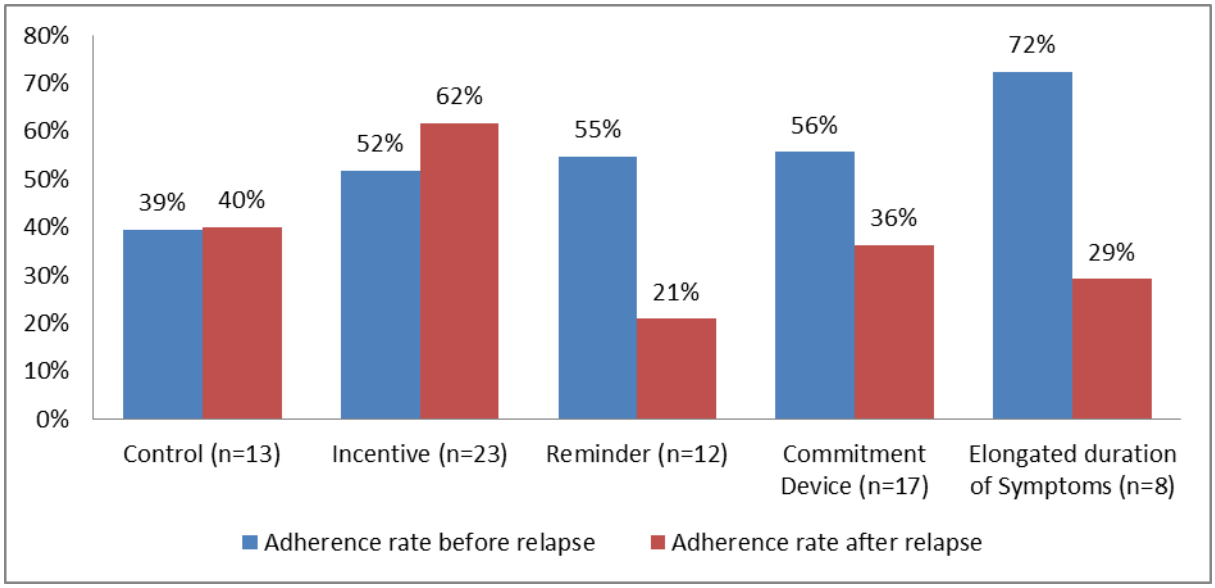
There was a significant decrease in adherence rates among all conditions (see table below).

condition	time	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
0	1	.783	.027	.730	.836
	2	.397	.040	.318	.476
1	1	.772	.025	.722	.821
	2	.476	.039	.398	.554
2	1	.868	.021	.826	.911
	2	.656	.031	.594	.718
3	1	.715	.025	.665	.766
	2	.459	.039	.381	.537
4	1	.844	.018	.808	.881
	2	.479	.051	.377	.580

These results seem to confirm my hypothesis that adherence rates drop significantly once the symptoms disappear. It substantiates the important role played by symptoms in the adherence to antibiotic medication.

5.10.5 Effect of relapse on adherence rates

The experiment included a consequence for non-adherence which was in the form of screen relapsing to being blurry. To recall, once the participant's screen was cleared, if he/she failed to enter the code, there was a 2% chance of "relapse" or of the screen becoming blurry by 25%. The probability of "relapse" doubled each time the code was not entered. There were 73 participants in total who experienced relapse (each of these participants only experienced relapse once). The plot below shows the adherence rates for these participants before and after relapse.



Adherence rates before and after relapse for the participants who experienced relapse

My expectation was that once a participant has experienced relapse, he/she would be more adherent but it seems that except for the incentive condition adherence rates dropped after relapse. However, there can be an explanation for this result. The table below shows the round when relapse occurred for different participants. It can be seen that for more than half the participants, relapse occurred when they only had one, two

or three code entries left. Since they knew that the game will end soon, they might have decided to forego entering the code and instead focus on the 2048 game. Since most participants experienced relapsed very close to the end of the experiment, drawing meaningful insight on the relationship between relapse and adherence rate might not be appropriate. Perhaps, in future experiments participants can be asked to play the same game again and then observe how adherence rates vary in relation to relapse.

Round when relapsed	Percent
7	4.1
8	5.5
9	4.1
10	19.2
11	8.2
12	16.4
13	21.9
14	20.5

5.10.6 Further analysis

One argument that can be made against this modelling experiment is that participants might have adopted a strategy whereby they enter the code to clear the screen and once the screen is cleared they cease to enter the code and maximize the time being spent to play the game, thereby maximize their earning in the experiment. This cannot be

imagined to be a dominant strategy in the real-world setting as patients do pay heed to the advice given by their doctors and have a high degree of trust and confidence in their doctors. Furthermore, patients do intend to take the medication as prescribed by their doctors. There were only 34 participants in the experiment who did not make any entry once their screen got cleared. This included 9 participants in the control condition, 10 participants in the incentive condition, 7 participants in the commitment device condition and 4 participants in the elongated duration for symptoms condition. Interestingly, there was no participant from the reminder condition among these 34 participants. If a participant was to adopt this strategy of ignoring the code entry then there does not seem to be a reason that why the reminder condition would not have such a participant since the reminder message only popped for a few seconds and the player could have ignored the reminder and continued with the game. I further excluded these 34 participants and ran the tests to observe whether there was any difference in the results obtained on the analysis regarding the relationship between adherence rate and symptoms, but the conclusion remained the same.

6 CHAPTER 6: Conclusion

In my PhD thesis I intended to carry out a behavioural diagnosis of the medication adherence problem through a theoretically informed framework and then develop a model to simulate the non-adherence behaviour. These constitute the first two stages of the Theory-Modelling-RCT cycle for developing behaviour change interventions. The results of the modelling experiment showed that having theoretically informed interventions increased the likelihood for them to be successful (both the incentive and reminder interventions that were tested in the modelling experiment came from the TDF analysis). Furthermore, modelling can also help in identifying which interventions are most likely to work in the RCT.

It is interesting to note that Theoretical Domains Framework (TDF) has only been used in the past with small to medium samples and my research is the first time that it has been administered at a national level. The results of the TDF generated many insights, a few of which led to development of treatment interventions for the modelling stage but future research work should follow up on modelling and testing the rest of the insights. For example, further investigation is required to understand how social influence plays a role in helping patients adhere to their medication regimen.

It is worth discussing how good the 2048 experiment has been in modelling the non-adherence behaviour. In Chapter 5 I discussed my observations and feedback from the participants of the pilot tests and the modelling experiment seemed to have generated the same feelings that are expressed by the patients such as forgetting to take the pill or adhering less the regimen once the symptoms disappear. The results of the modelling

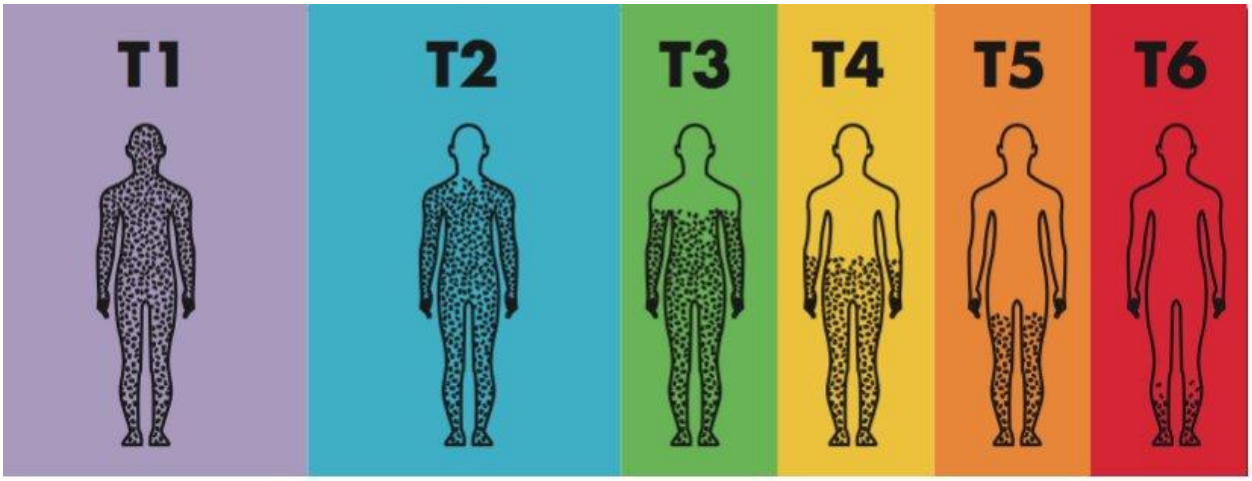
experiment reflect this behaviour of patients quite closely among the participants as well. The adherence rate found among the control group of the game experiment was 44% which is quite similar to the adherence rate found among patients. Although this statistic in its own does not allow us to completely ascertain the goodness of fit of the model, but had the adherence rate in control group been very low or very high it wouldn't have reflected well on showing that the 2048 experiment has been able to model the non-adherence behaviour.

The results of the modelling experiment showed that providing incentive improved the adherence rate. Providing incentive was chosen as one of the treatment conditions because the TDF analysis showed that there was a lack of reinforcement for patients to continue adhering to their antibiotic medication once the symptoms disappeared. There is evidence that incentives do help in improving medication adherence (discussed in Section 5.3.2.2.2), and the same was confirmed in the modelling experiment. Similarly, there is evidence that the use of reminders improve the medication adherence rates for patients (discussed in Section 5.3.2.2.3), and the same results were found in the modelling experiment.

While both the use of incentives and reminders increased the adherence rate in the modelling experiments (as has been predicted by multitude of studies before) I wanted to turn the tables and model an intervention that was yet to be carried out in the real-world setting. This motivated my selection of the use of commitment devices as one of the treatment groups in the modelling experiment. I used the same protocol that was followed by the Department of Health and Boots UK in their RCT (this has been discussed in Section 5.3.2.2.4) and the results showed that commitment sticker did not

improve adherence rates of the participants in the modelling experiment. Interestingly, a few months later when the results of the RCT came out it was found that the commitment sticker did not bring about any improvement in the adherence rates among patients as well. From the results obtained in the modelling experiment and their comparison with real-world analogues it seems that the modelling experiment was able to simulate the non-adherence behaviour of the patients.

The last treatment group of 'Elongated duration for symptoms' really shows the power of modelling experiment where we test a what-if scenario that is extremely difficult to test in an RCT setting. The results from the experiment provide a proof of concept that if symptoms last longer people adhere more to their medication regimen. A wild idea that comes to mind is that maybe the pills can be made in such a way that they keep the patients feeling sick until the last day of their treatment. Although, one behavioural consultancy based in India is testing an intervention along these lines. They are working on the issue of non-adherence of tuberculosis medication (which is an antibiotic medication but for a six month period) and have come across the same issue that patients stop taking their pills once the symptoms disappear. Rather than making people keep feeling sick (which is an extreme interpretation of the modelling experiment finding), they introduced an intervention to make patients realise that they are still sick even though the symptoms are gone (see image below).



Communicating to the patients visually that even though symptoms are gone the bacterial infection still remains inside the body

The treatment interventions that were tested for the modelling experiment were part informed by the TDF analysis and part to show the goodness of fit of the model and its advantages. Among the treatment conditions that were tested, it seems that reminders are the most effective in increasing adherence rates. However, it does not make sense to jump right into developing an RCT to test reminders with patients. In this PhD thesis, I did not aim to identify which intervention or combination of interventions can be the most effective in increasing medication adherence but rather to develop a model that can provide a platform to test various interventions and select the most effective ones to be included in a RCT. It is quite possible that an intervention is successful in a RCT but not acceptable by the target group. I would suggest that once we know from the modelling experiment which interventions show promise we should carry out a reality check with the target group and understand how accepting they would be if that intervention was rolled out. I will discuss one example here to make my argument. The modelling experiment showed that reminders worked really well in increasing

adherence rates, and the next logical step seems to be to test reminders in a RCT with patients. However, if a survey is carried out asking patients that would they be interested in receiving reminders to help them adhere to their medication course and it turns out that patients are not interested then it might not even make sense to carry out a RCT to test reminders. In a recent study, researchers conducted a RCT to assess the value of text message reminders as a means to improve medication adherence in patients receiving treatment for the prevention of a cardiovascular disease (Wald et al., 2014). They found that reminders improved adherence rate by 16%, but the interesting point to note is that for this study they contacted 7,004 patients and only 303 agreed to receive text reminders. Although the study showed that reminders significantly improved adherence rates of the patients, but the participant numbers also hint that many patients might not be interested in this service if it were to be rolled out. Hence, it is important to think about the acceptability of an intervention at the time of selecting interventions that are carried forward from the modelling stage to the RCT stage.

For my PhD thesis, I set up the first behavioural science lab in Pakistan. I was keen on having the general public as my participants and I knew that none of them would ever have participated in an experiment before, making them more receptive to the task. Using a game in the experiment proved to be a very important factor in attracting participants and greatly improved their engagement. As I said earlier, I had many participants requesting to play the game again because they enjoyed it. I believe that more attention should be paid by researchers on how to keep the participants engaged when designing an experiment.

Developing behaviour change interventions is a complex process and thus requires a systematic way to approach the problem. The process should start from developing a theoretical understanding of the behaviour at hand followed by modelling the behaviour to identify the exact mechanisms that might bring about the desired behaviour change. Once the most suitable interventions are identified in the modelling stage then a RCT should be carried out to test the intervention in the real-world setting. In this dissertation, I have showed how this process can be followed in relation to the problem of non-adherence to antibiotic medication. Care must always be taken in extrapolating results from the lab to the real world, and caution is particularly called for when the lab model abstracts away from some important features such as the feelings of the patients or the environment in which patients are making their decisions. However, generating hypothesis through simple modelling experiments can help us in developing the most effective interventions that can then be tested in the real-world setting (through RCT).

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8 Appendix

8.1 Appendix 1

PARTICIPANT INFORMATION LEAFLET

Study Title: Decision Making Study

Investigator(s): Umar Taj, Daniel Read, Ivo Vlaev

Introduction

You are invited to take part in a research study. Before you decide, you need to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully. Talk to others about the study if you wish.

(Part 1 tells you the purpose of the study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study)

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

What is the study about?

We would like to understand how people make decisions in a game setting.

Do I have to take part?

It is entirely up to you. We will describe the study and go through this information sheet, which we will give you to keep. If you choose to participate, we will ask you to sign a consent form to confirm that you have agreed to take part (if part of this study is an online or postal questionnaire/survey, by returning a completed questionnaire/survey, you are giving your consent for the information that you have

supplied to be used in this study and formal signed consent will not be collected where postal or online questionnaires/surveys are concerned). You will be free to withdraw at any time, without giving a reason and this will not affect you or your circumstances in any way.

What will happen to me if I take part?

You will be playing a modified version of a game called 2048. In this game you combine numbered tiles (using the up-down-right-left arrow keys) in an attempt to reach 2048.

What are the possible disadvantages, side effects, risks, and/or discomforts of taking part in this study?

There are no physical risks beyond normal computer use

What are the possible benefits of taking part in this study?

We are excited about what we can learn from the data collected in this study and we will use the information to improve our understanding of human decision making. The research also has applications for use in public policy and industry.

Expenses and payments

You will receive Rs. 80 show-up fees and can earn up to a maximum of Rs. 500 based on how well you perform in the game.

What will happen when the study ends?

We will be analysing the data collected to understand how people in general make decisions.

Will my taking part be kept confidential?

Yes. We will follow strict ethical and legal practice and all information about you will

be handled in confidence. Further details are included in Part 2.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm that you might suffer will be addressed. Detailed information is given in Part 2.

This concludes Part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

Who is organising and funding the study?

The study is being organised and funded by researchers at Warwick Business School.

What will happen if I don't want to carry on being part of the study?

Participation in this study is entirely voluntary. Refusal to participate will not affect you in any way. If you decide to take part in the study, you will need to sign a consent form, which states that you have given your consent to participate.

If you agree to participate, you may nevertheless withdraw from the study at any time without affecting you in any way.

You have the right to withdraw from the study completely and decline any further contact by study staff after you withdraw.

What if there is a problem?

This study is covered by the University of Warwick's insurance and indemnity cover.

If you have an issue, please contact the Chief Investigator of the study:

Daniel Read

Behavioural Science Group

Warwick Business School

Coventry CV4 7AL

United Kingdom

Email: daniel.read@wbs.ac.uk

Who should I contact if I wish to make a complaint?

Should anyone have any complaints relating to a study conducted at the University or by Warwick University's employees or students, the complainant should be advised to contact the Director of Delivery Assurance, details as below:

Director of Delivery AssuranceRegistrar's Office

University House

University of Warwick

Coventry CV4 8UW

Telephone: 024 7657 4774

Email: complaints@warwick.ac.uk

Will my taking part be kept confidential?

Your performance in this study is completely confidential and will be stored anonymously. Your identity will not be shared with anyone else. Data will be kept securely after the study. The form signed at the end of the study is just for the accounts department to keep track of the University's funds.

What will happen to the results of the study?

The data that will be collected in this study may be used to publish in an academic journal.

Who has reviewed the study?

This study has been reviewed and given favourable opinion by the University of Warwick's Humanities and Social Science Research Ethics Committee (HSSREC):

What if I want more information about the study?

If you have any questions about any aspect of the study, or your participation in it, not answered by this participant information leaflet, please contact:

Daniel Read

Behavioural Science Group

Warwick Business School

Coventry CV4 7AL

United Kingdom

Email: daniel.read@wbs.ac.uk

Thank you for taking the time to read this participant information leaflet.

HUMANITIES AND SOCIAL SCIENCE ETHICS COMMITTEE CONSENT FORM

Study Number:

Title of Project: Decision Making Study

Name of Researcher(s): Umar Taj, Daniel Read, Ivo Vlaev

Please initial all boxes

I confirm that I have read and understand the information sheet dated [DATE] f
above study. I have had the opportunity to consider the information, ask questio
have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at
time without giving any reason, without my medical, social care, education, or le
rights* (**delete as appropriate*) being affected. ☐

I agree to take part in the above study. ☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

8.2 Appendix 2

Patient Exit Interview Questionnaire

(Introduction by interviewer):

Hello. I am from Gallup Pakistan (show the official badge). We are carrying out a study on understanding the communication that takes place between the doctor and patient when the patient comes to see a doctor. In this study we are interviewing patients who have seen a doctor in the last 2 months.

A. *Have you seen a doctor in the last 2 months?*
    a. *Yes (Please proceed)*
    b. *No (exit the interview)*

I'd like to ask you a few questions regarding your communication with the doctor. Your input will be treated strictly confidential but it will provide a valuable contribution to a better understanding of what doctors communicate to their patients.

Section A (includes NICE antibiotic guideline)

What did the doctor diagnose? What did the doctor tell you about your health problem? Basically what did the doctor say you have or is wrong? (Write the response in the space below):

---

1. *Did the doctor tell you what medicine to take? (Read out options)*
    a. *Yes*
    b. *No*

2. *Did the doctor tell you how often to take the medicine every day? (Read out options)*
    a. *Yes*
    b. *No*

3. *Did the doctor tell you how long you should take the medicine for? (Read out options)*
    a. *Yes*
    b. *No*

4. *Did the doctor inform you about consequences of not completing the course? (Read out options)*
    a. *Yes*
    b. *No*

5. *Did the doctor discuss the benefits and harms of the medicine? (Read out options)*

a. *Yes*

b. *No*

6. *Did the doctor discuss what you should do if your condition deteriorates as a result of the medication? (Read out options)*

    a. *Yes*

    b. *No*

7. *Did the doctor tell you that you must complete the whole course and not leave it half way through? (Read out options)*

    a. *Yes*

    b. *No*

Section B (includes NICE TB guideline)

1. *Did the doctor educate you about your disease? (Read out options)*

    a. *Yes*

    b. *No*

Section C (from WIN Survey)

(Show Card A)

Note: Code but do not read out – here and throughout the interview: ***99 Doesn't apply***

Q. In your meeting, how good was that doctor at each of the following?

(Read out and code one answer for each)

1. *Giving you enough time*
    a. *Very good*
    b. *Good*
    c. *Neither good nor poor*
    d. *Poor*
    e. *Very poor*
    f. *Doesn't apply*
2. *Listening to you*
    a. *Very good*
    b. *Good*
    c. *Neither good nor poor*
    d. *Poor*
    e. *Very poor*
    f. *Doesn't apply*

3. *Explaining tests and treatments*
    a. *Very good*
    b. *Good*
    c. *Neither good nor poor*
    d. *Poor*
    e. *Very poor*

f. *Doesn't apply*

4. *Involving you in decisions about your care*
    a. *Very good*
    b. *Good*
    c. *Neither good nor poor*
    d. *Poor*
    e. *Very poor*
    f. *Doesn't apply*
5. *Treating you with care and concern*
    a. *Very good*
    b. *Good*
    c. *Neither good nor poor*
    d. *Poor*
    e. *Very poor*
    f. *Doesn't apply*

Q.Do you have confidence and trust in the doctor you saw or spoke to?

(Read out all options)

a. *Yes, definitely*
b. *Yes, to some extent*
c. *No, not at all*

8.3 Appendix 3

Domain	Construct	Item
D1 Knowledge	Knowledge (3)	I am aware of the content and objectives of [innovation/guideline]
		I know the content and objectives of [innovation/guideline]
		I am familiar with the content and objectives of [innovation/guideline]
	Procedural knowledge (3)	I am aware of how to [A] in [C, T] with [Ta]
		I know how to [A] in [C, T] with [Ta]
		I am familiar with how to [A] in [C, T] with [Ta]
D2 Skills	Skills (4)	I have been trained how to [A] in [C, T] with [Ta]
		I have the proficiency to [A] in [C, T] with [Ta]
		I have the skills to [A] in [C, T] with [Ta]
		I have practiced [A] in [C, T] with [Ta]
D3 Social/professional role and identity	Professional role (4)	[A] in [C, T] with [Ta] is part of my work as a [profession]
		As a [profession], it is my job to [A] in [C,

		T] with [Ta]
		It is my responsibility as a [profession] to [A] in [C, T] with [Ta]
		Doing [A] in [C, T] with [Ta] is consistent with my [profession]
D4 Beliefs about capabilities	Self-efficacy (2)	I am confident that I can [A] in [C, T] with [Ta] even when [Ta] is not motivated
		I am confident that I can [A] in [C, T] with [Ta] even when there is little time
	Perceived behavioral control (4)	I am confident that if I wanted I could [A] in [C, T] with [Ta]
		How much control do you have over [A] in [C, T] with [Ta]?
		For me, [A] in [C, T] with [Ta] is… (Very difficult – very easy)
		For me, [A] in [C, T] with [Ta] is… (Impossible – possible)
D5 Optimism	Optimism (3)	With regard to [A] in [C, T] with [Ta] in uncertain times, I usually expect the best
		With regard to [A] in [C, T] with [Ta] I'm always optimistic about the future
		With regard to [A] in [C, T] with [Ta]

		overall, I expect more good things to happen than bad
	Pessimism (3)	With regard to [A] in [C, T] with [Ta] if something can go wrong, it will
		With regard to [A] in [C, T] with [Ta] I hardly ever expect things to go my way
		With regard to [A] in [C, T] with [Ta] I rarely count on good things happening to me
D6 Beliefs about consequences	Attitudes (2)	For me, [A] in [C, T] with [Ta] is… (Useless – useful)
		For me, [A] in [C, T] with [Ta] is… (bad – good)
	Outcome expectancies (2)	If I [A] in [C, T] with [Ta] it will benefit public health
		If I [A] in [C, T] with [Ta] it will have disadvantages for my relationship with [Ta]
D7 Reinforcement	Reinforcement (3)	Whenever I [A] in [C, T] with [Ta], I get financial reimbursement
		Whenever I [A] in [C, T] with [Ta], I get recognition from professionals who are important to me

		Whenever I [A] in [C, T] with [Ta, I feel like I am making a difference
D8 Intentions	Intention (4)	For how many of the next 10 [Ta] do you intend to [A] in [C]?
		I will definitely [A] in [C] with [Ta] in the next [T]
		I intend to [A] in [C] with [Ta] in the next [T]
		How strong is your intention to [A] with [Ta] in [C] in the next [T]?
D9 Goals	Action planning (4)	I have a clear plan of how I will [A] in [C, T] with [Ta]
		I have a clear plan under what circumstances I will [A] in [C, T] with [Ta]
		I have a clear plan when I will [A] in [C, T] with [Ta]
		I have a clear plan how often I will [A] in [C, T] with [Ta]
	Priority (4)	Generally, in [C, T] with [Ta], how often is covering something else on your agenda a higher priority than [A]
		Generally, in [C, T] with [Ta], how often

		does covering something else on your agenda take precedence over [A]
		Generally, in [C, T] with [Ta], how often is covering something else on your agenda more urgent than [A]
		Generally, in [C, T] with [Ta], how often is covering something else on your agenda more pressing than [A]
D10 Memory, attention and decision processes	Memory (4)	[A] in [C, T] with [Ta] is easy to remember
		How often do you forget [A] in [C, T] with [Ta]?
		How often do you have to check the [innovation/guideline] before [A] in [C, T] with [Ta]?
		To what extent do you know [innovation/guideline] by heart to [A] in [C, T] with [Ta]?
	Attention (4)	When I need to concentrate to [A] in [C, T] with [Ta], I have no trouble focusing my attention
		When I am working hard on [A] in [C, T]

		with [Ta], I still get distracted by events around me
		When trying to focus my attention on [A] in [C, T] with [Ta], I have difficulty blocking out distracting thoughts
		When concentrating on [A] in [C, T] with [Ta], I can focus my attention so that I become unaware of what's going on around me
D11 Environmental context and resources	Resources/material (8)	[Innovation/guideline] has a good fit with routine practice
		[Innovation/guideline] provides the possibility to adapt it to the [Ta]'s needs (e.g., culture)
		In the organization I work [A] in [C, T] with [Ta] is routine
		In the organization I work there is enough time to [A] in [C, T] with [Ta]
		Within the socio-political context there is sufficient financial support (e.g., from local authorities, insurance companies, the government) for

		[innovation/guideline]
		Within the socio-political context there are good networks between parties involved in [innovation/guideline]
		Prior to delivery of [innovation/guideline] professionals are provided with a training to [A] in [C, T] with [Ta]
		During the delivery of [innovation/guideline] professionals are provided with sufficient financial reimbursement to [A] in [C, T] with [Ta]
D12 Social influences	Social support (4)	I can rely on the team of professionals with whom I deliver [innovation] when things get tough on [A] in [C, T] with [Ta]
		My colleagues are willing to listen to my problems related to [A] in [C, T] with [Ta]
		The team of professionals with whom I deliver [innovation] is helpful in getting [A] in [C, T] with [Ta] done
		I can rely on my colleagues when things get tough on [A] in [C, T] with [Ta]

	Subjective norm (2)	Most people who are important to me think that I should [A] in [C, T] with [Ta]
		Most people whose opinion I value would approve me of [A] in [C, T] with [Ta]
	Descriptive norm (2)	The team of professionals with whom I deliver [innovation/guideline] [A] in [C, T] with [Ta]
		Respected colleagues [A] in [C, T] with [Ta]
D13 Emotion	Affect (2)	Thinking about yourself and how you normally feel as a professional that delivers [innovation/guideline], to what extent do you generally feel inspired with regard to [A] in [C, T] with [Ta]
		Thinking about yourself and how you normally feel as a professional that delivers [innovation/guideline], to what extent do you generally feel nervous with regard to [A] in [C, T] with [Ta]
	Stress (2)	Have you recently, during the past two weeks been able to enjoy your normal day-to-day activities?
		Have you recently, during the past two

		weeks been feeling unhappy and depressed?
D14 Behavioral regulation	Automaticity (2)	[A] in [C, T] with [Ta] is something I do automatically
		[A] in [C, T] with [Ta] is something I do without thinking
	Self-monitoring (4)	I keep track of my overall progress towards [A] in [C, T] with [Ta]
		I tend to notice my successes while working towards [A] in [C, T] with [Ta]
		I am aware of my day-to-day behaviour as I work towards [A] in [C, T] with [Ta]
		I check regularly whether I am getting closer to attaining [A] in [C, T] with [Ta]
	Action planning (4)	I have a clear plan of how I will [A] in [C, T] with [Ta]
		I have a clear plan under what circumstances I will [A] in [C, T] with [Ta]
		I have a clear plan when I will [A] in [C, T] with [Ta]
		I have a clear plan how often I will [A] in [C, T] with [Ta]

Note. [A], action; [C], context; [T], time; [Ta], target

8.4 Appendix 4

8.4.1 Antimicrobial Resistance (AMR)

8.4.1.1 What is AMR?

Antimicrobial Resistance (AMR) arises when the micro-organisms that cause infection (for example, bacteria) survive exposure to a medicine that would normally kill them or stop their growth. This creates an opportunity for the strains that are capable of surviving exposure to a particular drug to grow and spread, due to lack of competition from the other strains that are affected by the medicine. This has led to the emergence of drug-resistant diseases such as multi drug resistant Tuberculosis (MDR TB) which is very difficult to treat and often communicable (for instance, if a patient has MDR TB then he/she can infect another person with MDR TB as well) (O'Neill, 2016).

There are various factors that have contributed towards the increase and acceleration of AMR such as misuse of medicines, poor infection control practices and global trade and travel (I discuss more about the various factors contributing to increase in AMR in Section 1.2.3.3). Among these factors, misuse of medicines stands out as an inherently behavioural problem. Misuse of medicines has primarily been taking place in two ways: over-prescription of medication and non-adherence to the completion of a medication course (Hallsworth et al., 2016). In this dissertation, I address the latter issue of non-adherence to the completion of a medication course.

8.4.1.2 How big a problem is it?

AMR is a particular concern in the domain of antibiotic usage. The increased resistance to the current antibiotic medications in the market mean that even minor surgeries and routine operations could become high risk procedures. Furthermore, procedures like organ transplantation and cancer chemotherapy could become ineffective as they require antibiotics to prevent and treat the bacterial infections that can be caused by the treatment (O'Neill, 2016).

The following three remarks from key leaders highlight the importance and magnitude of AMR:

"If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine" – David Cameron, former UK Prime Minister

"We have reached a critical point and must act now on a global scale to slow down antimicrobial resistance" – Professor Dame Sally Davies, UK Chief Medical Officer

"Antimicrobial resistance is a crisis that must be managed with the utmost urgency. As the world enters the ambitious new era of sustainable development, we cannot allow hard-won gains for health to be eroded by the failure of our mainstay medicines." - Dr Margaret Chan, Director General, World Health Organization

There is already a rise of drug resistant infections with numbers suggesting that up to 50,000 lives are lost each year to antibiotic-resistant infections in Europe and the US alone. Globally, at least 700,000 die each year of drug resistance in illnesses such as bacterial infections, malaria, HIV/AIDS or tuberculosis. KPMG and RAND carried out a

scenario analysis looking at what the world would look like in 2050 if the status quo is maintained and concluded that without any policies and effort to stop AMR, by 2050 we will have more than 10 million deaths every year due to AMR (O'Neill, 2016).

Not only are there these tragic human costs, AMR also poses real economic cost, which will continue to grow if the issue of AMR is not tackled. The KPMG and RAND scenario analysis estimates that the cost in terms of lost global production between now and 2050 would be a 100 trillion USD if no action is taken against AMR.

There has been some criticism of the estimates suggested by the scenario analysis for being exaggerated but it is more likely for the estimates to be too small (O'Neill, 2016). This can be the case because the scenario analysis did not take into account the secondary effects of AMR such as the risks in carrying out what are now deemed as normal surgical procedures such as caesarean sections or hip replacements.

8.4.1.3 Why is AMR increasing?

The increase in the prevalence of AMR can be contributed to various factors and below I explain the key factors.

- **Availability of cheap and over the counter antibiotics:** One factor contributing to the rise of AMR is simply the greater use of antibiotics in the population primarily owing to them being available cheaply. This is a bigger concern in countries where patients can simply buy drugs over the counter without medical prescriptions such as Pakistan and India.
- **Unnecessary prescription of antibiotics:** Another important driver for increased resistance is the prescription of antibiotic when they are not clinically

indicated (Hallsworth et al., 2016). Primary care is a focus for many antibiotic stewardship programs for three reasons: firstly, large proportions of antibiotic prescriptions come from primary care; secondly, there has been evidence linking increased resistance to the prescribing practices of the healthcare professionals; and thirdly, significant variation is found in the prescribing practices of the healthcare professionals providing an opportunity to address this issue (Costelloe et al., 2010; Hawker et al., 2014; Public Health England, 2014)

- **Non-adherence to the medication course by patients:** Once an antibiotic has been prescribed, failure to complete the medication course increases the risks of developing resistance. Patient's failure to complete the antibiotic medication allows the drug resistant strains to proliferate. I have already discussed at the start of this chapter how a patient's adherence to his/her medication regimen is generally low, hence making non-adherence to antibiotic medication one of the main factors contributing towards increased resistance (O'Neill, 2016).
- **Overuse and unnecessary use of antibiotics among animals:** The discussion of increased AMR often ignores the role played by the use of antibiotics among animals. In fact, there is more use of antibiotics among animals than humans. The process of developing AMR among animals is the same as that among humans and one of the main contributing factors to the increase of AMR among the human population is through the transfer of drug resistant strains (present among animals) to humans through food (O'Neill, 2016).
- **Lack of rapid diagnostics:** There is a lot of pressure on GPs to provide a treatment once a patient has explained his/her symptoms. Ideally an antibiotic

medication should be prescribed once the presence of a bacterial infection has been confirmed. However, the existing technology takes around a week to provide analysis of blood cultures. The expectation of the patients to be prescribed a medication for their illness and lack of rapid diagnostics means that sometimes GPs inadvertently end up prescribing antibiotics even though infection might have been viral (O'Neill, 2016).